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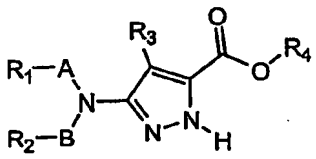
(54) Title: 5-AMINOPYRAZOLE CARBOXYLIC ACID DERIVATIVES AND METHODS OF TREATMENT OF METABOLIC-RELATED DISORDERS THEREOF



(I)

(57) Abstract: The present invention relates to certain pyrazole carboxylic acid or ester derivatives of Formula (I) and pharmaceutically acceptable salts thereof which exhibit useful pharmacological properties, for example, as agonists for the GPCR referred to herein as RUP38. Also provided by the present invention are pharmaceutical compositions containing compounds of the invention, and methods of using the compounds and compositions of the invention in the treatment of metabolic-related disorders, such as, dyslipidemia, atherosclerosis, coronary heart disease, insulin resistance, type 2 diabetes, Syndrome-X and the like. In addition, the present invention also provides for the use of the compounds of the invention in combination with other active agents such as those belonging to the class of -glucosidase inhibitors, aldose reductase inhibitors, biguanides, HMG-CoA reductase inhibitors, squalene synthesis inhibitors, fibrates, LDL catabolism enhancers, angiotensin converting enzyme (ACE) inhibitors, insulin secretion enhancers and the like.

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5-AMINO-1H-PYRAZOLE-3-CARBOXYLIC ACID DERIVATIVES AS AGONSITS FOR THE G-PROTEIN COUPLED RECEPTOR (GPCR) RUP38 FOR THE TREATMENT OF?METABOLIC-RELATED DISORDERS

FIELD OF THE INVENTION

The present invention relates to certain pyrazole carboxylic acid or ester derivatives of Formula (I) and pharmaceutically acceptable salts thereof which exhibit useful pharmacological properties, for example, as agonists for the G protein-coupled receptor (GPCR) referred to herein as **RUP38**.

Also provided by the present invention are pharmaceutical compositions containing compounds of the invention, and methods of using the compounds and compositions of the invention in the treatment of metabolic-related disorders, including dyslipidemia, atherosclerosis, coronary heart disease, insulin resistance, obesity, impaired glucose tolerance, atheromatous disease, hypertension, stroke, Syndrome X, heart disease, type 2 diabetes, hypo-HDL related atherosclerotic risk, ischemic cerebrovascular disease, peripheral vascular disease, stroke, myocardial infarction and the like. In addition, the present invention also provides for the use of the compounds of the invention in combination with other active agents such as those belonging to the class of α-glucosidase inhibitors, aldose reductase inhibitors, biguanides, HMG-CoA reductase inhibitors, squalene synthesis inhibitors, fibrates, LDL catabolism enhancers, angiotensin converting enzyme (ACE) inhibitors, insulin secretion enhancers, insulin secretion enhancers, thiazolidinediones, DP receptor antagonists and the like.

BACKGROUND OF THE INVENTION

Antilipolytic Agents

Atherosclerosis and stroke are the numbers one and number three leading causes of death of both men and women in the United States. Type 2 diabetes is a public health problem that is serious, widespread and increasing. Elevated levels of low density lipoprotein (LDL) cholesterol or low levels of high density lipoprotein (HDL) cholesterol are, independently, risk factors for atherosclerosis and associated cardiovascular pathologies. In addition, high levels of plasma free fatty acids are associated with insulin resistance and type 2 diabetes. One strategy for decreasing LDL-cholesterol, increasing HDL-cholesterol, and decreasing plasma free fatty acids is to inhibit lipolysis in adipose tissue. This approach involves regulation of hormone sensitive lipase, which is the rate-limiting enzyme in lipolysis. Lipolytic agents increase cellular levels of cAMP, which leads to activation of hormone sensitive lipase within adipocytes. Agents that lower intracellular cAMP levels, by contrast, would be antilipolytic.

It is also worth noting in passing that an increase in cellular levels of cAMP down-regulates the secretion of adiponectin from adipocytes [Delporte, ML et al. Biochem J (2002) July; the disclosure of which is incorporated by reference in its entirety]. Reduced levels of

plasma adiponectin have been associated with metabolic-related disorders, including atherosclerosis, coronary heart disease, insulin resistance, type 2 diabetes, hypertension and obseity [Matsuda, M et al. J Biol Chem 2002, 277, 37487-37491; Kazumi, T. et al. Metabolism 2004, 53, 589-93; Katsuya, I. Y., et al. Hypertension 2004, (May 3) Epub ahead of print; Qi, Y. et al. Nature Medicine published on line, 11 April 2004; Yamauchi, T. Nature 2003, 423, 762-769; Yamauchi T. et al. J Biol Chem. 2003, 278, 2461-2468; the disclosures of which are incorporated by reference in their entirety].

Compounds of the invention inhibit the production and release of free fatty acids from adipose tissue, likely via an inhibition of adenylyl cyclase, a decrease in intracellular cAMP levels, and a concomitant decrease in hormone sensitive lipase activity. Agonists that down-regulate hormone sensitive lipase activity leading to a decrease in plasma free fatty acid levels are likely to have therapeutic value. The consequence of decreasing plasma free fatty acids is two-fold. First, it will ultimately lower LDL-cholesterol and raise HDL-cholesterol levels, independent risk factors, thereby reducing the risk of mortality due to cardiovascular incidence subsequent to atheroma formation. Second, it will provide an increase in insulin sensitivity in individuals with insulin resistance or type 2 diabetes.

Agonists of antilipolytic GPCRs having limited tissue distribution beyond adipose may be especially valuable in view of the diminished opportunity for potentially undesirable side-effects.

Agents Raising HDL Chloesterol

It is widely believed that HDL is a "protective" lipoprotein [Gloria Lena Vega and Scott Grundy, Current Opinion in Lipidology, 7, 209-216 (1996)] and that increasing plasma levels of HDL may offer a direct protection against the development of atherosclerosis. Numerous studies have demonstrated that both the risk of coronary heart disease (CHD) in humans and the severity of experimental atherosclerosis in animals are inversely correlated with serum HDL-cholesterol (HDL-C) concentrations [Russ et al., Am. J. Med., 11, 480-483 (1951); Gofman et al., Circulation, 34, 679-697 (1966); Miller and Miller, Lancet, 1, 16-19 (1975); Gordon et al., Circulation, 79, 8-15 (1989); Stampfer et al., N. Engl. J. Med. 325, 373-381 (1991); Badimon et al., Lab. Invest., 60, 455-461 (1989)]. Atherosclerosis is the process of the accumulation of cholesterol within the arterial wall which results in the occlusion, or stenosis, of coronary and cerebral arterial vessels and subsequent myocardial infarction and stroke. Angiographic studies have shown that elevated levels of some HDL particles in humans appear to be correlated to a decreased number of sites of stenosis in the coronary arteries of humans (Miller et al., Br. Med. J., 282, 1741-1744 (1981)).

There are several mechanisms by which HDL may protect against the progression of atherosclerosis. Studies in vitro have shown that HDL is capable of removing cholesterol from cells (Picardo et al., Arteriosclerosis, 6, 434-441 (1986)). Data of this nature suggest that one

antiatherogenic property of HDL may lie in its ability to deplete tissue of excess free cholesterol and eventually lead to the delivery of this cholesterol to the liver (Glomset, J. Lipid Res., 9, 155-167 (1968)). This has been supported by experiments showing efficient transfer of cholesterol from HDL to the liver (Glass et al., J. Biol. Chem., 258 7161-7167 (1983); McKinnon et al., J. Biol. Chem., 26, 2548-2552 (1986)). In addition, HDL may serve as a reservoir in the circulation for apoproteins necessary for the rapid metabolism of triglyceride-rich lipoproteins (Grow and Fried, J. Biol. Chem., 253, 1834-1841 (1978); Lagocki and Scanu, J. Biol. Chem., 255, 3701-3706 (1980); Schaefer et al., J. Lipid Res., 23, 1259-1273 (1982)).

Generally, the Total Cholesterol/HDL-Cholesterol (i.e., TC/HDL) ratio represents a useful predictor as to the risk of an individual in developing a more serious condition, such as a HDL-related condition. The classification of plasma lipid levels is shown in Table A:

TABLE A

CLASSIFICATION OF PLASMA LIPID LEVELS

TOTAL CHOLESTEROL	**< about 200 mg/dl**	**Desirable**
	about 200 to about 239 mg/dl	**Borderline High**
	> about 240 mg/dl	**High**
HDL-CHOLESTEROL	**< about 40 mg/dl**	**Low (Men)**
	< about 50 mg/dl	**Low (Women)**
	> about 60 mg/dl	**High**

From: 2001 National Cholesterol Education Program Guidelines

Accordingly, the recommended Total Cholesterol/HDL-Cholesterol (i.e., TC/HDL) ratio indicates that a ratio of about 3.5 or less is ideal and a ratio of about 4.5 or greater is considered an increased "at risk." The value of determining the TC/HDL ratio is clearly evident in the circumstance where an individual presents with "normal" LDL and total cholesterol but possesses low HDL-cholesterol. Based on LDL and total cholesterol the individual may not qualify for treatment, however, factor in the HDL-cholesterol level then a more accurate risk assessment may be obtained. Thus, if the individual's level of HDL-cholesterol is such that the ratio is greater than about 4.5 then therapeutic intervention may be warranted. A physician or care provider may determine the need of treatment based on a TC/HDL ratio; for example, a TC/HDL ratio of about 2.5 or greater, about 3.0 or greater, about 3.5 or greater, about 4.0 or greater, about 4.5 or greater, about 5.0 or greater, or a TC/HDL ratio of about 5.5 or greater.

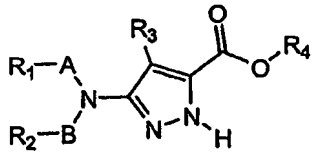
Accordingly, agents that increase HDL levels or reduce total cholesterol/HDL ratios would be of great importance as antiatherosclerotic agents, and particularly useful in the treatment of coronary heart disease, ischemic cerebrovascular disease, peripheral vascular disease,

dyslipoproteinimias and other HDL-related diseases.

Summary of the Invention

The present invention is drawn to compounds which bind to and interact with the GPCR defined as **RUP38** and uses thereof. The term **RUP38**, as used herein, includes the human sequences found in GeneBank accession number D10923.1, naturally-occurring allelic variants, mammalian orthologs, biologically active fragments and recombinant mutants thereof.

One aspect of the present invention encompasses certain carboxylic acid or ester derivatives as shown in Formula (I):



(I)

or a pharmaceutically acceptable salt, solvate or hydrate thereof;

wherein:

A is a C_{1-3} alkylene optionally substituted with 1, 2, 3, or 4 substituents selected independently from the group consisting of C_{1-6} alkoxy, C_{1-6} alkyl, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonyl, amino, C_{1-6} alkylamino, C_{2-6} dialkylamino, carbo-C_{1-6}-alkoxy, carboxy, cyano, C_{3-6} cycloalkyl, halogen, C_{1-6} haloalkoxy, C_{1-6} haloalkyl, C_{1-6} haloalkylsulfinyl, C_{1-6} haloalkylsulfonyl, C_{1-6} haloalkylthio and hydroxyl;

B is a C_{1-3} alkylene optionally substituted with 1, 2, 3, or 4 substituents selected independently from the group consisting of C_{1-6} alkoxy, C_{1-6} alkyl, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonyl, amino, C_{1-6} alkylamino, C_{2-6} dialkylamino, carbo-C_{1-6}-alkoxy, carboxy, cyano, C_{3-6} cycloalkyl, halogen, C_{1-6} haloalkoxy, C_{1-6} haloalkyl, C_{1-6} haloalkylsulfinyl, C_{1-6} haloalkylsulfonyl, C_{1-6} haloalkylthio and hydroxyl, or B is a bond;

R_1 is H, aryl, heteroaryl, C_{1-6} alkyl, C_{3-7} cycloalkyl, C_{2-6} alkenyl, or C_{1-6} haloalkyl, wherein the R_1 is optionally substituted with 1, 2, 3, 4, or 5 substituents selected independently from the group consisting of C_{1-6} acyl, acyloxy, C_{2-6} alkenyl, C_{1-6} alkoxy, C_{1-6} alkyl, C_{1-6} alkylcarboxamido, C_{2-6} alkynyl, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonyl, C_{1-6} alkylthio, C_{1-6} alkylureyl, amino, C_{1-6} alkylamino, C_{2-6} dialkylamino, carbo-C_{1-6}-alkoxy, carboxy, cyano, C_{3-6} cycloalkyl, C_{2-6} dialkylcarboxamido, halogen, C_{1-6} haloalkoxy, C_{1-6} haloalkyl, C_{1-6} haloalkylsulfinyl, C_{1-6} haloalkylsulfonyl, C_{1-6} haloalkylthio, hydroxyl, nitro and thiol, or two adjacent substituents together with the carbon atoms to which they are bonded form a C_{5-7} cycloalkyl or C_{5-7} heterocycloalkyl optionally substituted with 1, 2, 3, or 4 halogen atoms;

R_2 is H, aryl, heteroaryl, C_{1-6} alkyl, C_{3-7} cycloalkyl, C_{2-6} alkenyl, or C_{1-6} haloalkyl, wherein the R_2 is optionally substituted with 1, 2, 3, 4, or 5 substituents selected independently

from the group consisting of C_{1-6} acyl, acyloxy, C_{2-6} alkenyl, C_{1-6} alkoxy, C_{1-6} alkyl, C_{1-6} alkylcarboxamido, C_{2-6} alkynyl, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonyl, C_{1-6} alkylthio, C_{1-6} alkylureyl, amino, C_{1-6} alkylamino, C_{2-6} dialkylamino, carbo-C_{1-6}-alkoxy, carboxy, cyano, C_{3-6} cycloalkyl, C_{2-6} dialkylcarboxamido, halogen, C_{1-6} haloalkoxy, C_{1-6} haloalkyl, C_{1-6} haloalkylsulfinyl, C_{1-6} haloalkylsulfonyl, C_{1-6} haloalkylthio, hydroxyl, nitro and thiol, or two adjacent substituents together with the carbon atoms to which they are bonded form a C_{5-7} cycloalkyl or C_{5-7} heterocycloalkyl optionally substituted with 1, 2, 3, or 4 halogen atoms;

R_3 is selected from the group consisting of H, C_{1-6} acyl, acyloxy, C_{2-6} alkenyl, C_{1-6} alkoxy, C_{1-6} alkyl, C_{1-6} alkylcarboxamido, C_{2-6} alkynyl, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonyl, C_{1-6} alkylthio, C_{1-6} alkylureyl, amino, C_{1-6} alkylamino, C_{2-6} dialkylamino, carbo-C_{1-6}-alkoxy, carboxy, cyano, C_{3-6} cycloalkyl, C_{2-6} dialkylcarboxamido, halogen, C_{1-6} haloalkoxy, C_{1-6} haloalkyl, C_{1-6} haloalkylsulfinyl, C_{1-6} haloalkylsulfonyl, C_{1-6} haloalkylthio, hydroxyl, nitro and thiol; and

R_4 is H or C_{1-6} alkyl.

In some embodiments, R_3 is selected from the group consisting of H, C_{1-6} acyl, acyloxy, C_{2-6} alkenyl, C_{1-6} alkoxy, C_{1-6} alkyl, C_{1-6} alkylcarboxamido, C_{2-6} alkynyl, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonyl, C_{1-6} alkylthio, C_{1-6} alkylureyl, amino, C_{1-6} alkylamino, C_{3-6} dialkylamino, carbo-C_{1-6}-alkoxy, carboxy, cyano, C_{3-6} cycloalkyl, C_{2-6} dialkylcarboxamido, halogen, C_{1-6} haloalkoxy, C_{1-6} haloalkyl, C_{1-6} haloalkylsulfinyl, C_{1-6} haloalkylsulfonyl, C_{1-6} haloalkylthio, hydroxyl, nitro and thiol.

Some embodiments of the present invention include a pharmaceutical composition comprising at least one compound of the present invention and a pharmaceutically acceptable carrier.

Some embodiments of the present invention include methods of modulating a **RUP38** receptor comprising contacting the receptor with an effective amount of a compound of the present invention, wherein "compound(s) of the present invention" is intended to include Formula (I) and subgenera thereof. In some embodiments the compound is an agonist of the **RUP38** receptor.

Some embodiments of the present invention include methods of modulating a **RUP38** receptor in an individual comprising contacting the receptor with a compound of the present invention. In some embodiments the compound is an agonist of the **RUP38** receptor. In some embodiments, the modulation of the **RUP38** receptor treats a metabolic-related disorder.

Some embodiments of the present invention include methods of modulating **RUP38** receptor function in a cell, tissue or individual comprising contacting the cell, tissue or individual with an effective amount of a compound of the present invention or a pharmaceutical composition thereof as described herein. In some embodiments, the **RUP38** receptor function is associated with a metabolic-related disorder.

Some embodiments of the present invention include methods of treatment of a metabolic-

related disorder comprising administering to an individual in need of such treatment a therapeutically effective amount of a compound of the present invention. In some embodiments, the metabolic-related disorder is selected from the group consisting of dyslipidemia, atherosclerosis, coronary heart disease, insulin resistance, obesity, impaired glucose tolerance, atheromatous disease, hypertension, stroke, Syndrome X, heart disease, type 2 diabetes, hypo-HDL related atherosclerotic risk, ischemic cerebrovascular disease, peripheral vascular disease, stroke, and myocardial infarction. In further embodiments, the metabolic-related disorder is selected from the group consisting of dyslipidemia, atherosclerosis, coronary heart disease, insulin resistance and type 2 diabetes. In still further embodiments, the metabolic-related disorder is dyslipidemia.

Some embodiments of the present invention include methods of raising HDL cholesterol levels in an individual comprising administering to the individual a therapeutically effective amount of a compound of of the present invention.

Some embodiments of the present invention include the use of compounds of the present invention for production of medicaments for use in the treatment of a metabolic disorder.

One aspect of the present invention pertains to compounds of the present invention as described herein, for use in methods of treatment of the human or animal body by therapy.

One aspect of the present invention pertains to compounds of the present invention as described herein, for use in a method of treatment of a metabolic-related disorder of the human or animal body by therapy. In some embodiments, the metabolic-related disorder is selected from the group consisting of dyslipidemia, atherosclerosis, coronary heart disease, insulin resistance, obesity, impaired glucose tolerance, atheromatous disease, hypertension, stroke, Syndrome X, heart disease, type 2 diabetes, hypo-HDL related atherosclerotic risk, ischemic cerebrovascular disease, peripheral vascular disease, stroke, and myocardial infarction. In further embodiments, the metabolic-related disorder is selected from the group consisting of dyslipidemia, atherosclerosis, coronary heart disease, insulin resistance and type 2 diabetes. In still further embodiments, the metabolic-related disorder is dyslipidemia.

One aspect of the present invention pertains to compounds of the present invention as described herein, for use in a method of raising HDL cholesterol levels of the human or animal body by therapy.

In some embodiments, the individual in certain methods is a mammal. In some embodiments, the mammal is a human.

Some embodiments of the present invention include methods of producing pharmaceutical compositions comprising admixing at least one compound according to any of the compound embodiments disclosed herein and a pharmaceutically acceptable carrier.

In some embodiments, the invention pertains to methods for alleviation of a symptom of any of the diseases, conditions or disorders mentioned herein.

Applicant reserves the right to exclude any one or more of the compounds from any of the embodiments of the invention. Applicant additionally reserves the right to exclude any disease, condition or disorder from any of the embodiments of the invention.

Brief Description of the Figures

Figure 1: Figure 1 shows histograms representing relative expression levels of **RUP38** detected in different human tissues *via* DNA microarray. The horizontal axis displays the different tissues, which are identified in Example 2(B) herein. The vertical axis indicates level of expression of **RUP38**. In Figure 1, note the high level of expression in primary adipocytes of **RUP38** (the signal toward the left of each of the histograms corresponding to primary adipocytes is identified by a vertical arrow above the bar, for ease of reference).

Figure 2: Figure 2 is a photograph of an ethidium bromide stained gel illustrating the relative expression of **RUP25** (a GPCR related to **RUP38**, GeneBank accession number AB065876.1) and **RUP38** as detected by RT-PCR using cDNA derived from a number of human tissues as template. Note the tissue expression for **RUP38** in adipocycte, spleen and lung; also notice by comparison with **RUP25**, **RUP38** has limited tissue distribution beyond adipose. The controls are shown in the far right three lanes.

Figure 3: Figure 3 depicts melanophores transfected with DNA plasmids expressing **RUP38** without treatment. These cells are pigment-aggregated because **RUP38** is a Gi-coupled receptor having a high basal level of activity, and therefore driving the aggregation to a measurable level in the absence of a ligand.

Figure 4: Figure 4 presents screening data via adenylyl cyclase assay for **RUP38**. Note that nicotinic acid does not activate inhibition of forskolin stimulated cAMP in **RUP38**-expressing CHO cells whereas 1-isopropyl-1*H*-benzotriazole-5-carboxylic acid does. 1-Isopropyl-1*H*-benzotriazole-5-carboxylic acid has no effect on CHO cells expressing **RUP25** or **RUP19** (an orphan GPCR also related to **RUP38**, GeneBank accession number AF345568.1). NT indicates not tested. The compound, 1-isopropyl-1*H*-benzotriazole-5-carboxylic acid, was identified as an agonist for **RUP38**.

Detailed Description of the Invention

Definitions

For clarity and consistency, the following definitions will be used throughout this patent document.

AGONISTS shall mean moieties that interact and activate the receptor, such as the **RUP38** receptor and initiates a physiological or pharmacological response characteristic of that receptor. For example, when moieties activate the intracellular response upon binding to the receptor, or enhance

GTP binding to membranes.

ANGINA PECTORIS is intended herein to encompass the paroxysmal thoracic pain caused generally and most often by myocardial anoxia as a result of atherosclerosis.

The term **ANTAGONISTS** is intended to mean moieties that competitively bind to the receptor at the same site as agonists (for example, the endogenous ligand), but which do not activate the intracellular response initiated by the active form of the receptor, and can thereby inhibit the intracellular responses by agonists or partial agonists. Antagonists do not diminish the baseline intracellular response in the absence of an agonist or partial agonist.

ATHEROSCLEROSIS is intended herein to encompass disorders of the arteries that result in the progressive accumulation of smooth muscle cells and lipids within the intima. Atherosclerosis is a disorder that is generally characterized by yellowish plaques of cholesterol, others lipids and cellular debris in the inner layers of the walls of the arteries. Over time the atherosclerotic plaque increases thus narrowing the lumen and reducing the blood flow to organs supplied by the artery. The plaque eventually creates a risk for thrombosis and is one of the major causes of coronary heart disease, angina pectoris, myocardial infarction and other disorders, such as, congestive heart failure, ischemic heart disease, peripheral vascular disease, stroke and the like.

CHEMICAL GROUP, MOIETY OR RADICAL:

The term "**C_{1-6} acyl**" denotes an alkyl radical attached to a carbonyl wherein the definition of alkyl has the same definition as described herein; some examples include formyl, acetyl, propionyl, butanoyl, iso-butanoyl, and the like.

The term "**C_{1-6} acyloxy**" denotes an acyl radical attached to an oxygen atom wherein acyl has the same definition has described herein; some examples include acetyloxy, propionyloxy, butanoyloxy, iso-butanoyloxy and the like.

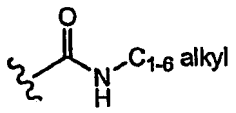
The term "**C_{2-6} alkenyl**" denotes a radical containing 2 to 4 carbons wherein at least one carbon-carbon double bond is present, some embodiments have 3 carbons, and some embodiments have 2 carbons. Both E and Z isomers and mixtures of E and Z isomers are embraced by the term "**alkenyl.**" Examples of an alkenyl include vinyl, allyl, 2-butenyl, 3-butenyl, and the like.

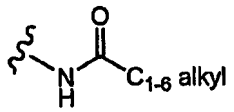
The term "**C_{1-6} alkoxy**" as used herein denotes a radical alkyl, as defined herein, attached directly to an oxygen atom. Examples include methoxy, ethoxy, n-propoxy, iso-propoxy, n-butoxy, t-butoxy, iso-butoxy and the like.

The term "**C_{1-8} alkyl**", "**C_{1-6} alkyl**", and "**C_{1-4} alkyl**" denote a straight or branched carbon radical containing 1 to 8 carbons, 1 to 6 carbons, or 1 to 4 carbons respectively, some embodiments are 1 to 3 carbons, and some embodiments are 1 or 2 carbons. Examples of an alkyl include, but not limited to, methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, t-butyl, sec-butyl, n-pentyl, iso-pentyl, sec-pentyl, neo-pentyl, pent-3-yl, 2-methyl-but-1-yl, 1,2-dimethyl-

prop-1-yl, n-hexyl, iso-hexyl, sec-hexyl, neo-hexyl, 1-ethyl-2-methyl-prop-1-yl, 1,2,2-trimethyl-prop-1-yl, 1,1,2-trimethyl-prop-1-yl, 1-ethyl-1-methyl-prop-1-yl, 1,1-dimethyl-but-1-yl, 1,2-dimethyl-but-1-yl, 2,3-dimethyl-but-1-yl, 2,2-dimethyl-but-1-yl, 1,3-dimethyl-but-1-yl, hex-3-yl, 2-methyl-pent-1-yl, 3-methyl-pent-1-yl, heptyl, 1-methyl-hexyl, 1-ethyl-pentyl, 1-propyl-butyl, octyl, 1-methyl-heptyl, 1-ethyl-hexyl, 1-propyl-pentyl, and the like.

The term "**C_{1-6} alkylcarboxamido**" denotes a single alkyl group attached to an amide, wherein alkyl has the same definition as found herein. The C_{1-6} alkylcarboxamido may be represented by the following:

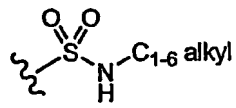


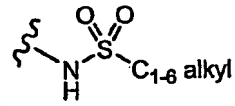


The term "**C_{1-6} alkylsulfinyl**" denotes an alkyl radical attached to a sulfoxide radical of the formula: -S(O)- wherein the alkyl radical has the same definition as described herein. Examples include methylsulfinyl, ethylsulfinyl and the like.

The term "**C_{1-3} alkylene**" refers to a divalent straight carbon group, such as, $-CH_2-$, $-CH_2CH_2-$, $-CH_2CH_2CH_2-$.

The term "**C_{1-6} alkylsulfonamide**" refers to the groups





The term "**C_{1-6} alkylsulfonyl**" denotes an alkyl radical attached to a sulfone radical of the formula: $-S(O)_2-$ wherein the alkyl radical has the same definition as described herein. Examples include methylsulfonyl, ethylsulfonyl and the like.

The term "**C_{1-6} alkylthio**" denotes an alkyl radical attached to a sulfide of the formula: -S- wherein the alkyl radical has the same definition as described herein. Examples include methylsulfanyl (i.e., CH_3S-), ethylsulfanyl, isopropylsulfanyl and the like.

The term "**C_{1-6} alkylamino**" denotes one alkyl radical attached to an amino radical wherein the alkyl radical has the same meaning as described herein. Some examples include methylamino, ethylamino, propylamino and the like.

The term "**C_{1-6} alkylureyl**" denotes the group of the formula: -NC(O)N- wherein one are both of the nitrogens are substituted with the same or different C_{1-6} alkyl group wherein alkyl has the same definition as described herein. Examples of an alkylureyl include, $CH_3NHC(O)NH-$, $NH_2C(O)NCH_3-$, $(CH_3)_2N(O)NH-$, $(CH_3)_2N(O)NH-$, $(CH_3)_2N(O)NCH_3-$, $CH_3CH_2NHC(O)NH-$, $CH_3CH_2NHC(O)NCH_3-$, and the like.

The term "**C_{2-6} alkynyl**" denotes a radical containing 2 to 6 carbons and at least one carbon-carbon triple bond, some embodiments are 2 to 4 carbons, some embodiments are 2 to 3 carbons, and some embodiments have 2 carbons. Examples of an alkynyl include ethynyl,

ethynyl, 1-propynyl, 2-propynyl, 1-butynyl, 2-butynyl, 3-butynyl, 1-pentynyl, 2-pentynyl, 3-pentynyl, 4-pentynyl, 1-hexynyl, 2-hexynyl, 3-hexynyl, 4-hexynyl, 5-hexynyl and the like. The term **"alkynyl"** includes di- and tri-ynes.

The term **"amino"** refers to $-NH_2$.

The term **"aryl"** denotes an aromatic ring radical containing 6 to 10 ring carbons. Examples include phenyl and naphthyl.

The term **"carbo-C_{1-6}-alkoxy"** refers to an alkyl ester of a carboxylic acid, wherein the alkyl group is C_{1-4}. Examples include carbomethoxy, carboethoxy, carboisopropoxy and the like.

The term **"carboxamide"** refers to the group $-CONH_2$.

The term **"carboxy"** refers to the group $-CO_2H$.

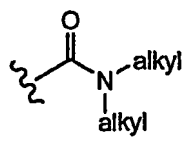
The term **"C_{3-7} cycloalkenyl"** denotes a non-aromatic ring radical containing 3 to 7 ring carbons and at least one double bond; some embodiments contain 5 to 7 carbons; some embodiments contain 3 to 6 carbons; some embodiments contain 3 to 5 carbons; some embodiments contain 3 to 4 carbons. Examples include cyclopropenyl, cyclobutenyl, cyclopentenyl, cyclopentenyl, cyclohexenyl, and the like.

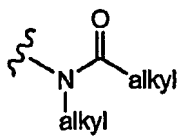
The term **"C_{3-7} cycloalkyl"** or **"C_{3-6} cycloalkyl"** denotes a non aromatic ring radical containing 3 to 7 carbons or 3 to 6 carbons respectively; some embodiments contain 5 to 7 carbons; some embodiments contain 3 to 5 carbons; some embodiments contain 3 to 4 carbons. Examples include cyclopropyl, cyclobutyl, cyclopentyl, cyclopenyl, cyclohexyl, cycloheptyl and the like.

The term **"cyano"** denotes the group $-CN$.

The term **"C_{2-6} dialkylamino"** denotes an amino substituted with two of the same or different alkyl radicals wherein alkyl radical has the same definition as described herein and the sum of the number of carbons between the two alkyl groups is 2 to 6. Some embodiments contain 3 to 6 carbons, wherein the sum of the number of carbons between the two alkyl groups is 3 to 6 (i.e., in some embodiments, C_{3-6} dialkylamino include dialkylamino groups other than dimethylamino). In general, examples include dimethylamino, methylethylamino, diethylamino, diethylamino, and the like.

The term **"C_{2-6} dialkylcarboxamido"** denotes two alkyl radicals, that are the same or different, attached to an amide group, wherein alkyl has the same definition as described herein. A C_{2-6} dialkylcarboxamido may be represented by the following groups:





;

wherein the sum of the number of carbons between the two alkyl groups is 2 to 6. Examples of a dialkylcarboxamide include *N,N*-dimethylcarboxamide, *N*-methyl-*N*-ethylcarboxamide, *N*-methyl-*N*-pentylcarboxamide and the like.

The term "**C_{1-6} haloalkoxy**" denotes a haloalkyl, as defined herein, that is directly attached to an oxygen to form a difluoromethoxy, trifluoromethoxy, 2,2,2-trifluoroethoxy, pentafluoroethoxy and the like.

The term "**C_{1-6} haloalkyl**" denotes an alkyl group, defined herein, wherein the alkyl is substituted with at least one halogen up to fully substituted represented by the formula C_nL_{2n+1}, wherein L is a halogen; when more than one halogen is present then they may be the same or different and selected from F, Cl, Br or I. Examples include fluoromethyl, difluoromethyl, trifluoromethyl, chlorodifluoromethyl, 2,2,2-trifluoroethyl, pentafluoroethyl and the like.

The term "**C_{1-6} haloalkylsulfinyl**" denotes a haloalkyl radical attached to a sulfoxide of the formula: -S(O)- wherein the alkyl radical has the same definition as described herein. Examples include trifluoromethylsulfinyl, 2,2,2-trifluoroethylsulfinyl, 2,2-difluoroethylsulfinyl and the like.

The term "**C_{1-6} haloalkylsulfonyl**" denotes a haloalkyl attached to a sulfone of the formula: $-S(O)_2-$ wherein haloalkyl has the same definition as described herein. Examples include trifluoromethylsulfonyl, 2,2,2-trifluoroethylsulfonyl, 2,2-difluoroethylsulfonyl and the like.

The term "**C_{1-6} haloalkylthio**" denotes an alkylthio radical substituted with one or more halogens. Examples include trifluoromethylthio, 1,1-difluoroethylthio, 2,2,2-trifluoroethylthio and the like.

The term "**halogen**" or "**halo**" denotes F, Cl, Br and I.

The term "**heteroaryl**" denotes an aromatic ring system that may be a single ring, two fused rings or three fused rings containing carbons and at least one ring heteroatom selected from O, S and N. Examples of heteroaryl groups include, but not limited to, pyridyl, pyrazinyl, pyridazinyl, pyrimidinyl, triazinyl, quinoline, benzoxazole, benzothiazole, 1*H*-benzimidazole, isoquinoline, quinazoline, quinoxaline, pyridinone and the like.

The term "**C_{5-7} heterocycloalkyl**" denotes a non-aromatic carbon ring (i.e., cycloalkyl or cycloalkenyl as defined herein) wherein one, two or three ring carbons are replaced by one, two or three heteroatoms, such as, O, S, S(O), $S(O)_2$, NH, and N-C_{1-4}-alkyl. Examples of a heterocycloalkyl include piperidinyl, morpholinyl, piperzinyl, pyrrolidinyl, and the like.

The term "**hydroxyl**" refers to the group -OH.

The term "**nitro**" denotes the group $-NO_2$.

The term "**thiol**" denotes the group –SH.

COMPOSITION shall mean a material comprising at least two compounds or two components; for example, and not limitation, a Pharmaceutical Composition is a Composition.

CONGESTIVE HEART FAILURE (CHF) shall refer to a disorder in which the heart loses its ability to pump blood efficiently. Congestive heart failure becomes more prevalent with advancing age. Ischemic heart disease is the most common cause of congestive heart failure, accounting for 60-70% of all cases. An increased venous pressure greater than 12 mmHg is one

of the major Framingham criteria for congestive heart failure, as is a reduction in cardiac output equivalent to a circulation time greater than 25 seconds.

CORONARY HEART DISEASE is intended herein to encompass disorders comprising a narrowing of the small blood vessels that supply blood and oxygen to the heart. CORONARY HEART DISEASE usually results from the build up of fatty material and plaque. As the coronary arteries narrow, the flow of blood to the heart can slow or stop. CORONARY HEART DISEASE can cause chest pain (stable angina), shortness of breath, heart attack, or other symptoms.

CONTACT or **CONTACTING** shall mean bringing the indicated moieties together, whether in an in vitro system or an in vivo system. Thus, "contacting" a **RUP38** receptor with a compound of the invention includes the administration of a compound of the present invention to an individual, preferably a human, having a **RUP38** receptor, as well as, for example, introducing a compound of the invention into a sample containing a cellular or more purified preparation containing a **RUP38** receptor.

HYPO-HDL RELATED ATHEROSCLEROTIC RISK as used herein refers to a HDL-related disorder that leads to or predisposes an individual to the risk of developing atherosclerosis (*supra*) by the presence of low levels of HDL cholesterol. Although low levels of HDL may depend on a variety of health factors, Table **B** can be used as a general guideline by physicians or caregivers in evaluating the individual.

TABLE B

HDL-CHOLESTEROL	**about 40 mg/dl or less**	**Low (Men)**
	about 50 mg/dl or less	**Low (Women)**

The levels in Table **B** are useful as a general guideline for evaluational purposes, levels outside these values may depend on a variety of health factors, all of which would be recognized by a physician or caregiver.

IN NEED OF SUCH TREATMENT as used herein refers to a judgment made by a caregiver (e.g. physician, nurse, nurse practitioner, etc. in the case of humans; veterinarian in the case of animals, including non-human mammals) that an individual or animal requires or will benefit from treatment. This judgment is made based on a variety of factors that are in the realm of a caregiver's expertise, but that includes the knowledge that the individual is ill, or will be ill, as the result of a disease, condition or disorder that is treatable by the compounds of the invention. The term "treatment" also refers in the alternative to "prophylaxis." Therefore, in general, "in need of treatment" refers to the judgment of the caregiver that the individual is already ill, accordingly, the compounds of the present invention are used to alleviate, inhibit or ameliorate the disease, condition or disorder. Furthermore, the phrase also refers, in the alternative, to the judgment made by the caregiver that the individual will become ill. In this context, the

compounds of the invention are used in a protective or preventive manner.

INDIVIDUAL as used herein refers to any animal, vertebrate, mammal and human; for example, mice, rats, other rodents, rabbits, dogs, cats, swine, cattle, sheep, horses, or primates, and humans. In some embodiments, individual refers to human.

ISCHEMIC HEART DISEASE shall refer to a disorder caused by lack of oxygen to the tissues of the heart, in which muscles of the heart are affected and the heart cannot pump properly. Ischemic heart disease is the most common cardiomyopathy in the United States.

MYOCARDIAL INFARCTION shall refer to the damage or death of an area of heart muscle because of an inadequate supply of oxygen to that area. Myocardial infarctions are often caused by a clot that blocks one of the coronary arteries (the blood vessels that bring blood and oxygen to heart muscle) or by a narrowing of an artery. The clot or narrowing of an artery prevents blood and oxygen from reaching that area of the heart, leading to the death of heart cells in that area.

PERIPHERAL VASCULAR DISEASE refers to disorders affecting the blood vessels outside the heart and brain, such as, arteries, veins, and lymphatics of the extremities. Peripheral vascular disease includes, but not limited to, peripheral artery disease (PAD), and the like.

PHARMACEUTICAL COMPOSITION shall mean a composition comprising at least one active ingredient, whereby the composition is amenable to investigation for a specified, efficacious outcome in a mammal (for example, and not limitation, a human). Those of ordinary skill in the art will understand and appreciate the techniques appropriate for determining whether an active ingredient has a desired efficacious outcome based upon the needs of the artisan.

STROKE occurs when the arterial blood flow leading to or in the brain becomes blocked or ruptures and a result of this sudden diminution or loss of blood, the individual's neurological function is decreased. Blood carries oxygen and nutrients to the neurons (nerve cells) in the brain, so when the blood flow stops, the cells begin to die. As a result, the functions of the body controlled by the nerve cells can lose their ability to function. Secondary brain damage resulting from the stroke can include cerebral cell destruction, or lesions, in the area surrounding the ischemic injury, in the case of focal ischemia, and also in areas of selective vulnerability in lesions, such as the hippocampus or basal ganglia, in the case of global ischemia. The secondary damage resulting from a stroke can often be manifested by functional impairment, such as but not limited to, loss of physical movement, loss of speech, loss of short-term and/or long-term memory.

THERAPEUTICALLY EFFECTIVE AMOUNT as used herein refers to the amount of active compound or pharmaceutical agent that elicits the biological or medicinal response in a tissue, system, animal, individual or human that is being sought by a researcher, veterinarian, medical doctor or other clinician, which includes one or more of the following:

(1) Preventing the disease; for example, preventing a disease, condition or disorder in an

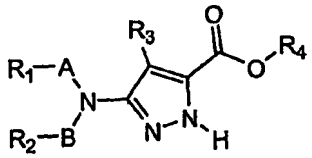
individual that may be predisposed to the disease, condition or disorder but does not yet experience or display the pathology or symptomatology of the disease,

(2) Inhibiting the disease; for example, inhibiting a disease, condition or disorder in an individual that is experiencing or displaying the pathology or symptomatology of the disease, condition or disorder (i.e., arresting further development of the pathology and/or symptomatology), and

(3) Ameliorating the disease; for example, ameliorating a disease, condition or disorder in an individual that is experiencing or displaying the pathology or symptomatology of the disease, condition or disorder (i.e., reversing the pathology and/or symptomatology).

Compounds of the Invention

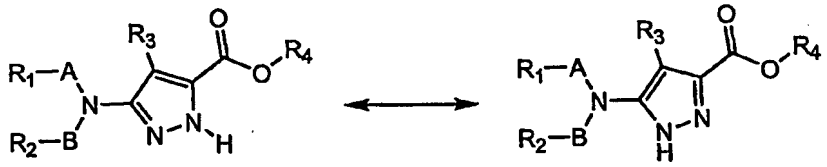
One aspect of the present invention encompasses certain pyrazole carboxylic acid or ester derivatives as shown in Formula (I):



(I)

or a pharmaceutically acceptable salt thereof, wherein R_1, R_2, R_3, R_4, A, and B are described herein *supra* and *infra*.

Compounds of the invention also include tautomeric forms, such as keto-enol tautomers, pyrazole tautomeric forms, and the like. One example is shown below for Compounds of Formulae (I) and (I'):



(I) (I')

Tautomeric forms can be in equilibrium or sterically locked into one form by appropriate substitution. It is understood that the various tautomeric forms are within the scope of the compounds of the present invention.

It is appreciated that certain features of the invention which are, for clarity, described in the context of separate embodiments, may also be provided in combination in a single embodiment. Conversely, various features of the invention which are, for brevity, described in the context of a single embodiment, may also be provided separately or in any suitable subcombination.

As used herein, "substituted" indicates that at least one hydrogen atom of the chemical group is replaced by a non-hydrogen substituent or group. When a chemical group herein is

"substituted" it may have up to the full valance of substitution; for example, a methyl group can be substituted by 1, 2, or 3 substituents, a methylene group can be substituted by 1 or 2 substituents, a phenyl group can be substituted by 1, 2, 3, 4, or 5 substituents, a naphthyl group can be substituted by 1, 2, 3, 4, 5, 6, or 7 substituents and the like. It is understood that when a group is optionally substituted with more than one group then those groups can be same or different.

Compounds of the invention can also include all isotopes of atoms occurring in the intermediates or final compounds. Isotopes include those atoms having the same atomic number but different mass numbers. For example, isotopes of hydrogen include deuterium and tritium.

In some embodiments, R_1 is H. In some embodiments, R_1 is H and A is C_{1-3} alkylene. In particular embodiments, R_1 and A together are selected from the group consisting of CH_3, CH_2CH_3, and $CH_2CH_2CH_3$.

In some embodiments, R_1 is aryl, heteroaryl, C_{1-6} alkyl, C_{3-7} cycloalkyl, C_{2-6} alkenyl, or C_{1-6} haloalkyl, wherein the R_1 is optionally substituted with 1, 2, 3, 4, or 5 substituents. In some embodiments, R_1 is optionally substituted with 1, 2, 3, or 4 substituents. In some embodiments, R_1 is optionally substituted with 1, 2, or 3 substituents. In some embodiments, R_1 is optionally substituted with 1, or 2 substituents.

In some embodiments, R_1 is aryl optionally substituted with 1, 2, 3, 4, or 5 substituents selected independently from the group consisting of C_{1-6} acyl, acyloxy, C_{2-6} alkenyl, C_{1-6} alkoxy, C_{1-6} alkyl, C_{1-6} alkylcarboxamido, C_{2-6} alkynyl, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonyl, C_{1-6} alkylthio, C_{1-6} alkylureyl, amino, C_{1-6} alkylamino, C_{2-6} dialkylamino, carbo-C_{1-6}-alkoxy, carboxy, cyano, C_{3-6} cycloalkyl, C_{2-6} dialkylcarboxamido, halogen, C_{1-6} haloalkoxy, C_{1-6} haloalkyl, C_{1-6} haloalkylsulfinyl, C_{1-6} haloalkylsulfonyl, C_{1-6} haloalkylthio, hydroxyl, nitro, and thiol.

In some embodiments, R_1 is aryl optionally substituted with 1, 2, 3, 4, or 5 substituents selected independently from the group consisting of C_{1-6} acyl, C_{2-6} alkenyl, C_{1-6} alkoxy, C_{1-6} alkyl, C_{1-6} alkylcarboxamido, C_{2-6} alkynyl, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonyl, C_{1-6} alkylthio, C_{1-6} alkylureyl, C_{1-6} alkylamino, C_{2-6} dialkylamino, carbo-C_{1-6}-alkoxy, carboxy, cyano, C_{3-6} cycloalkyl, C_{2-6} dialkylcarboxamido, halogen, C_{1-6} haloalkoxy, C_{1-6} haloalkyl, C_{1-6} haloalkylsulfinyl, C_{1-6} haloalkylsulfonyl, hydroxyl, and nitro.

In some embodiments, R_1 is aryl optionally substituted with 1, 2, 3, 4 or 5 substituents selected independently from the group consisting of C_{1-6} acyl, C_{1-6} alkoxy, C_{1-6} alkyl, C_{1-6} alkylamino, C_{2-6} dialkylamino, carbo-C_{1-6}-alkoxy, carboxy, cyano, halogen, C_{1-6} haloalkoxy, C_{1-6} haloalkyl, hydroxyl and nitro.

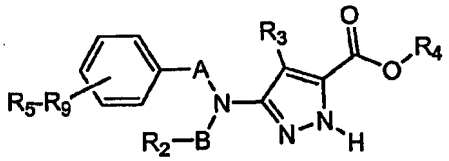
In some embodiments, R_1 is aryl optionally substituted with 1, 2, 3, 4 or 5 substituents selected independently from the group consisting of C_{1-6} alkoxy, C_{1-6} alkyl, carboxy, cyano, halogen, C_{1-6} haloalkoxy, and C_{1-6} haloalkyl.

In some embodiments, R_1 is aryl optionally substituted with halogen. In some

embodiments, R_1 is aryl optionally substituted with F.

In some embodiments, R_1 is phenyl.

In some embodiments, R_1 is phenyl and compounds can be represented by Formula (Ib) as shown below:

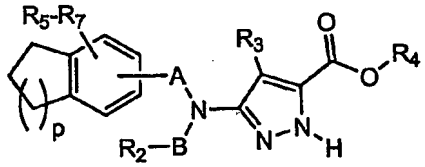


(Ib)

wherein each variable in Formula (Ib) has the same meaning as described herein, and R_5-R_9 are each independently selected from the group consisting of H, C_{1-6} acyl, acyloxy, C_{2-6} alkenyl, C_{1-6} alkoxy, C_{1-6} alkyl, C_{1-6} alkylcarboxamido, C_{2-6} alkynyl, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonyl, C_{1-6} alkylthio, C_{1-6} alkylureyl, amino, C_{1-6} alkylamino, C_{2-6} dialkylamino, carbo-C_{1-6}-alkoxy, carboxy, cyano, C_{3-6} cycloalkyl, C_{2-6} dialkylcarboxamido, halogen, C_{1-6} haloalkoxy, C_{1-6} haloalkyl, C_{1-6} haloalkylsulfinyl, C_{1-6} haloalkylsulfonyl, C_{1-6} haloalkylthio, hydroxyl, nitro, and thiol.

In some embodiments, R_1 is aryl optionally substituted with two adjacent substituents together with the aryl form a C_{5-7} cycloalkyl optionally substituted with halogen.

In some embodiments, R_1 is phenyl optionally substituted with two adjacent substituents together with the aryl to form a C_{5-7} cycloalkyl optionally substituted with halogen. In some embodiments, compounds of the present invention can be represented by Formula (Id) as shown below:



(Id)

wherein each variable in Formula (Id) has the same meaning as described herein, and "p" is 1, 2, or 3.

In some embodiments, R_1 is aryl optionally substituted with two adjacent substituents together with the aryl to form a C_{5-7} heterocycloalkyl optionally substituted with halogen. In some embodiments, compounds of the present invention can be represented by Formula (Id) wherein 1, or 2 non-aromatic ring carbons are independently replaced with a heteroatom selected from the group consisting of O, S, S(O), $S(O)_2$, NH, and N-C_{1-4}-alkyl.

In some embodiments, R_1 is a benzo[1,3]dioxolyl.

In some embodiments, R_1 is a benzo[1,3]dioxol-4-yl.

In some embodiments, R_1 is heteroaryl optionally substituted with 1, 2, 3, or 4 substituents selected independently from the group consisting of C_{1-6} acyl, acyloxy, C_{2-6} alkenyl, C_{1-6} alkoxy, C_{1-6} alkyl, C_{1-6} alkylcarboxamido, C_{2-6} alkynyl, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonyl,

C_{1-6} alkylthio, C_{1-6} alkylureyl, amino, C_{1-6} alkylamino, C_{2-6} dialkylamino, carbo-C_{1-6}-alkoxy, carboxy, cyano, C_{3-6} cycloalkyl, C_{2-6} dialkylcarboxamido, halogen, C_{1-6} haloalkoxy, C_{1-6} haloalkyl, C_{1-6} haloalkylsulfinyl, C_{1-6} haloalkylsulfonyl, C_{1-6} haloalkylthio, hydroxyl, nitro and thiol.

In some embodiments, R_1 is heteroaryl optionally substituted with 1, 2, 3, or 4 substituents selected independently from the group consisting of C_{1-6} acyl, C_{2-6} alkenyl, C_{1-6} alkoxy, C_{1-6} alkyl, C_{1-6} alkylcarboxamido, C_{2-6} alkynyl, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonyl, C_{1-6} alkylthio, C_{1-6} alkylureyl, C_{1-6} alkylamino, C_{2-6} dialkylamino, carbo-C_{1-6}-alkoxy, carboxy, cyano, C_{3-6} cycloalkyl, C_{2-6} dialkylcarboxamido, halogen, C_{1-6} haloalkoxy, C_{1-6} haloalkyl, C_{1-6} haloalkylsulfinyl, C_{1-6} haloalkylsulfonyl, hydroxyl, nitro and thiol.

In some embodiments, R_1 is heteroaryl optionally substituted with 1, 2, 3, or 4 substituents selected independently from the group consisting of C_{1-6} acyl, C_{1-6} alkoxy, C_{1-6} alkyl, C_{1-6} alkylamino, C_{2-6} dialkylamino, carbo-C_{1-6}-alkoxy, carboxy, cyano, halogen, C_{1-6} haloalkoxy, C_{1-6} haloalkyl, hydroxyl and nitro.

In some embodiments, R_1 is heteroaryl optionally substituted with 1, 2, 3, or 4 substituents selected independently from the group consisting of C_{1-6} alkoxy, C_{1-6} alkyl, carboxy, cyano, halogen, C_{1-6} haloalkoxy, and C_{1-6} haloalkyl.

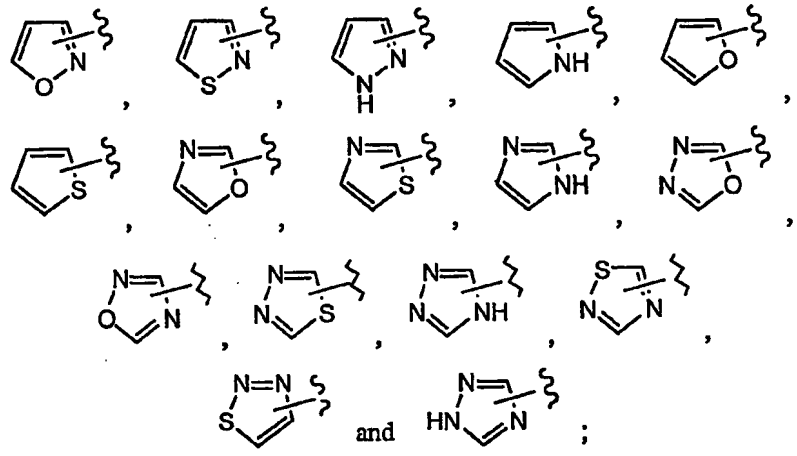
In some embodiments, R_1 is heteroaryl optionally substituted with 1, 2, 3, or 4 substituents selected independently from the group consisting of C_{1-6} alkyl, and halogen. In some embodiments, R_1 is heteroaryl optionally substituted with 1, 2, 3, or 4 substituents selected independently from the group consisting of CH_3, F, Cl, and Br.

In some embodiments, R_1 is a 5-member or 6-member heteroaryl.

In some embodiments, R_1 is a 5-member heteroaryl.

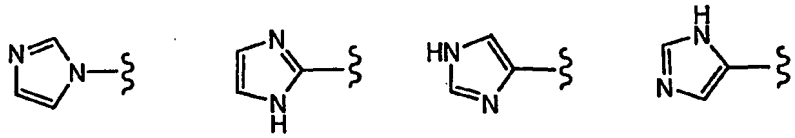
In some embodiments, the heteroaryl is selected from the group in **Table 2** as shown below:

TABLE 2



wherein the 5-membered heteroaryl is bonded at any available position of the ring, for example, a

imidazolyl ring can be bonded at one of the ring nitrogens (i.e., imidazol-1-yl group) or at one of the ring carbons (i.e., imidazol-2-yl, imidazol-4-yl or imiadazol-5-yl group) as illustrated below:



imidazol-1-yl imidazol-2-yl imidazol-4-yl imidazol-5-yl

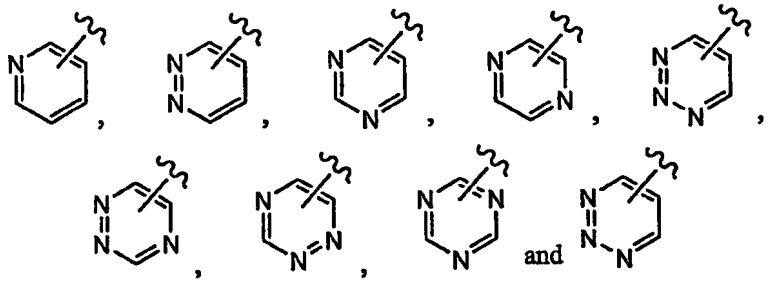
In some embodiments, R_1 is a 5-member heteroaryl selected from the group consisting of a furanyl, an isoxazolyl, an oxazolyl, an [1,2,4]-oxadiazolyl, an [1,3,4]-oxadiazolyl, a thienyl, an isothiazolyl, a thiazolyl, a [1,2,4]-thiadiazolyl, a [1,3,4-thiadiazolyl, a 1H-pyrrolyl, a 1H-pyrazolyl, an 1H-imidazolyl, a 1H-[1,2,4]-triazolyl, a 1H-[1,2,4]-triazolyl, and a 1H-tetrazolyl.

In some embodiments, R_1 is a 5-member heteroaryl selected from the group consisting of thien-2-yl, thien-3-yl, furan-2-yl and furan-3-yl. It is understood that due to variations in chemical nomenclature that a group may have more than one chemical name to represent the group, for example, thien-2-yl is equivalent to thiophen-2-yl. Other examples exist in the art and those of ordinary skill are credited with the ability to recognize that they are present.

In some embodiments, the heteroaryl is a 6-member heteroaryl.

In some embodiments, the heteroaryl is selected from the group in **Table 3** as shown below:

TABLE 3



wherein the heteroaryl group is bonded at any ring carbon.

In some embodiments, R_1 is a 6-member heteroaryl selected from the group consisting of a pyridyl, a pyrazine, and a pyrimidinyl.

In some embodiments, R_1 is a 6-member selected from the group consisting of pyridin-2-yl, pyridin-3-yl, and pyridin-4-yl.

In some embodiments, R_1 is C_{1-6} alkyl optionally substituted with 1, 2, 3, 4 or 5 substituents selected independently from the group consisting of C_{1-6} acyl, acyloxy, C_{2-6} alkenyl, C_{1-6} alkoxy, C_{1-6} alkyl, C_{1-6} alkylcarboxamido, C_{2-6} alkynyl, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonyl, C_{1-6} alkylthio, C_{1-6} alkylureyl, amino, C_{1-6} alkylamino, C_{2-6} dialkylamino, carbo-C_{1-6}-alkoxy, carboxy, cyano, C_{3-6} cycloalkyl, C_{2-6} dialkylcarboxamido, halogen, C_{1-6} haloalkoxy, C_{1-6}

haloalkyl, C_{1-6} haloalkylsulfinyl, C_{1-6} haloalkylsulfonyl, C_{1-6} haloalkylthio, hydroxyl, nitro, and thiol.

In some embodiments, R_1 is C_{1-6} alkyl optionally substituted with 1, 2, 3, 4 or 5 substituents selected independently from the group consisting of C_{1-6} acyl, C_{2-6} alkenyl, C_{1-6} alkoxy, C_{1-6} alkyl, C_{1-6} alkylcarboxamido, C_{2-6} alkynyl, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonyl, C_{1-6} alkylthio, C_{1-6} alkylureyl, C_{1-6} alkylamino, C_{2-6} dialkylamino, carbo-C_{1-6}-alkoxy, carboxy, cyano, C_{3-6} cycloalkyl, C_{2-6} dialkylcarboxamido, halogen, C_{1-6} haloalkoxy, C_{1-6} haloalkyl, C_{1-6} haloalkylsulfinyl, C_{1-6} haloalkylsulfonyl, hydroxyl and nitro.

In some embodiments, R_1 is C_{1-6} alkyl optionally substituted with 1, 2, 3, 4 or 5 substituents selected independently from the group consisting of C_{1-6} acyl, C_{1-6} alkoxy, C_{1-6} alkyl, C_{1-6} alkylamino, C_{2-6} dialkylamino, carbo-C_{1-6}-alkoxy, carboxy, cyano, halogen, C_{1-6} haloalkoxy, C_{1-6} haloalkyl, hydroxyl and nitro.

In some embodiments, R_1 is C_{1-6} alkyl optionally substituted with 1, 2, 3, 4 or 5 substituents selected independently from the group consisting of C_{1-6} alkoxy, C_{1-6} alkyl, carboxy, cyano, halogen, C_{1-6} haloalkoxy, and C_{1-6} haloalkyl.

In some embodiments, R_1 is C_{3-7} cycloalkyl optionally substituted with 1, 2, 3, 4 or 5 substituents selected independently from the group consisting of C_{1-6} alkoxy, C_{1-6} alkyl, carboxy, cyano, halogen, C_{1-6} haloalkoxy, and C_{1-6} haloalkyl.

In some embodiments, R_1 is C_{2-6} alkenyl optionally substituted with 1, 2, 3, 4 or 5 substituents selected independently from the group consisting of C_{1-6} acyl, acyloxy, C_{2-6} alkenyl, C_{1-6} alkoxy, C_{1-6} alkyl, C_{1-6} alkylcarboxamido, C_{2-6} alkynyl, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonyl, C_{1-6} alkylthio, C_{1-6} alkylureyl, amino, C_{1-6} alkylamino, C_{2-6} dialkylamino, carbo-C_{1-6}-alkoxy, carboxy, cyano, C_{3-6} cycloalkyl, C_{2-6} dialkylcarboxamido, halogen, C_{1-6} haloalkoxy, C_{1-6} haloalkyl, C_{1-6} haloalkylsulfinyl, C_{1-6} haloalkylsulfonyl, C_{1-6} haloalkylthio, hydroxyl, nitro and thiol.

In some embodiments, R_1 is C_{2-6} alkenyl optionally substituted with 1, 2, 3, 4 or 5 substituents selected independently from the group consisting of C_{1-6} alkoxy, C_{1-6} alkyl, carboxy, cyano, halogen, C_{1-6} haloalkoxy, and C_{1-6} haloalkyl.

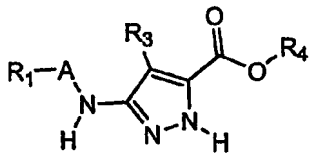
In some embodiments, R_1 is C_{1-6} haloalkyl optionally substituted with 1, 2, 3, 4 or 5 substituents selected independently from the group consisting of C_{1-6} acyl, acyloxy, C_{2-6} alkenyl, C_{1-6} alkoxy, C_{1-6} alkyl, C_{1-6} alkylcarboxamido, C_{2-6} alkynyl, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonyl, C_{1-6} alkylthio, C_{1-6} alkylureyl, amino, C_{1-6} alkylamino, C_{2-6} dialkylamino, carbo-C_{1-6}-alkoxy, carboxy, cyano, C_{3-6} cycloalkyl, C_{2-6} dialkylcarboxamido, halogen, C_{1-6} haloalkoxy, C_{1-6} haloalkylsulfinyl, C_{1-6} haloalkylsulfonyl, C_{1-6} haloalkylthio, hydroxyl, nitro and thiol.

In some embodiments, R_1 is C_{1-6} haloalkyl optionally substituted with 1, 2, 3, 4 or 5 substituents selected independently from the group consisting of C_{1-6} alkoxy, C_{1-6} alkyl, carboxy, cyano, halogen, and C_{1-6} haloalkoxy.

In some embodiments, R_2 is H.

In some embodiments, R_2 is H and A is C_{1-3} alkylene. In particular embodiments, R_2 and A together are selected from the group consisting of CH_3, CH_2CH_3, $CH_2CH_2CH_3$.

In some embodiments, R_2 is H and A is a bond. In some embodiments, compounds of the present invention can be presented by Formula (If):



(If)

wherein each variable in Formula (If) has the same meaning as described herein.

In some embodiments, R_2 is aryl, heteroaryl, C_{1-6} alkyl, C_{3-7} cycloalkyl, C_{2-6} alkenyl, or C_{1-6} haloalkyl, wherein the R_2 is optionally substituted with 1, 2, 3, 4, or 5 substituents. In some embodiments, R_2 is optionally substituted with 1, 2, 3, or 4 substituents. In some embodiments, R_2 is optionally substituted with 1, 2, or 3 substituents. In some embodiments, R_2 is optionally substituted with 1, or 2 substituents.

In some embodiments, R_2 is aryl optionally substituted with 1, 2, 3, 4, or 5 substituents selected independently from the group consisting of C_{1-6} acyl, acyloxy, C_{2-6} alkenyl, C_{1-6} alkoxy, C_{1-6} alkyl, C_{1-6} alkylcarboxamido, C_{2-6} alkynyl, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonyl, C_{1-6} alkylthio, C_{1-6} alkylureyl, amino, C_{1-6} alkylamino, C_{2-6} dialkylamino, carbo-C_{1-6}-alkoxy, carboxy, cyano, C_{3-6} cycloalkyl, C_{2-6} dialkylcarboxamido, halogen, C_{1-6} haloalkoxy, C_{1-6} haloalkyl, C_{1-6} haloalkylsulfinyl, C_{1-6} haloalkylsulfonyl, C_{1-6} haloalkylthio, hydroxyl, nitro, and thiol.

In some embodiments, R_2 is aryl optionally substituted with 1, 2, 3, 4, or 5 substituents selected independently from the group consisting of C_{1-6} acyl, C_{2-6} alkenyl, C_{1-6} alkoxy, C_{1-6} alkyl, C_{1-6} alkylcarboxamido, C_{2-6} alkynyl, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonyl, C_{1-6} alkylthio, C_{1-6} alkylureyl, C_{1-6} alkylamino, C_{2-6} dialkylamino, carbo-C_{1-6}-alkoxy, carboxy, cyano, C_{3-6} cycloalkyl, C_{2-6} dialkylcarboxamido, halogen, C_{1-6} haloalkoxy, C_{1-6} haloalkyl, C_{1-6} haloalkylsulfinyl, C_{1-6} haloalkylsulfonyl, hydroxyl, and nitro.

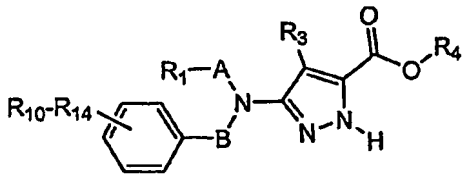
In some embodiments, R_2 is aryl optionally substituted with 1, 2, 3, 4 or 5 substituents selected independently from the group consisting of C_{1-6} acyl, C_{1-6} alkoxy, C_{1-6} alkyl, C_{1-6} alkylamino, C_{2-6} dialkylamino, carbo-C_{1-6}-alkoxy, carboxy, cyano, halogen, C_{1-6} haloalkoxy, C_{1-6} haloalkyl, hydroxyl and nitro.

In some embodiments, R_2 is aryl optionally substituted with 1, 2, 3, 4 or 5 substituents selected independently from the group consisting of C_{1-6} alkoxy, C_{1-6} alkyl, carboxy, cyano, halogen, C_{1-6} haloalkoxy, and C_{1-6} haloalkyl.

In some embodiments, R_2 is aryl optionally substituted with halogen. In some embodiments, R_2 is aryl optionally substituted with F.

In some embodiments, R_2 is phenyl.

In some embodiments, R_2 is phenyl and compounds can be represented by Formula (**Ih**) as shown below:



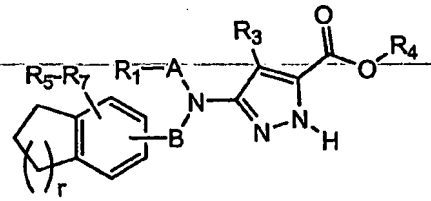
(**Ih**)

wherein each variable in Formula (**Ih**) has the same meaning as described herein, and R_{10}-R_{14} are each independently selected from the group consisting of H, C_{1-6} acyl, acyloxy, C_{2-6} alkenyl, C_{1-6} alkoxy, C_{1-6} alkyl, C_{1-6} alkylcarboxamido, C_{2-6} alkynyl, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonyl, C_{1-6} alkylthio, C_{1-6} alkylureyl, amino, C_{1-6} alkylamino, C_{2-6} dialkylamino, carbo-C_{1-6}-alkoxy, carboxy, cyano, C_{3-6} cycloalkyl, C_{2-6} dialkylcarboxamido, halogen, C_{1-6} haloalkoxy, C_{1-6} haloalkyl, C_{1-6} haloalkylsulfinyl, C_{1-6} haloalkylsulfonyl, C_{1-6} haloalkylthio, hydroxyl, nitro, and thiol.

In some embodiments, R_2 is aryl optionally substituted with two adjacent substituents together with the aryl to form a C_{5-7} cycloalkyl optionally substituted with halogen.

In some embodiments, R_2 is phenyl optionally substituted with two adjacent substituents together with the aryl to form a C_{5-7} cycloalkyl optionally substituted with halogen.

In some embodiments, compounds of the present invention can be represented by Formula (**Ij**) as shown below:



(**Ij**)

wherein each variable in Formula (**Ij**) has the same meaning as described herein, and "r" is 1, 2, or 3.

In some embodiments, R_2 is aryl optionally substituted with two adjacent substituents together with the aryl to form a C_{5-7} heterocycloalkyl optionally substituted with halogen. In some embodiments, compounds of the present invention can be represented by Formula (**Ij**) wherein 1, or 2 non-aromatic ring carbons are independently replaced with a heteroatom selected from the group consisting of O, S, S(O), $S(O)_2$, NH, and N-C_{1-4}-alkyl.

In some embodiments, R_2 is a benzo[1,3]dioxolyl.

In some embodiments, R_2 is a benzo[1,3]dioxol-4-yl.

It is understood that when the C_{5-7} cycloalkyl or C_{5-7} heterocycloalkyl is substituted with more than one halogen, they can either be the same halogen or different halogens.

In some embodiments, R_2 is heteroaryl optionally substituted with 1, 2, 3, or 4 substituents selected independently from the group consisting of C_{1-6} acyl, acyloxy, C_{2-6} alkenyl,

C_{1-6} alkoxy, C_{1-6} alkyl, C_{1-6} alkylcarboxamido, C_{2-6} alkynyl, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonyl, C_{1-6} alkylthio, C_{1-6} alkylureyl, amino, C_{1-6} alkylamino, C_{2-6} dialkylamino, carbo-C_{1-6}-alkoxy, carboxy, cyano, C_{3-6} cycloalkyl, C_{2-6} dialkylcarboxamido, halogen, C_{1-6} haloalkoxy, C_{1-6} haloalkyl, C_{1-6} haloalkylsulfinyl, C_{1-6} haloalkylsulfonyl, C_{1-6} haloalkylthio, hydroxyl, nitro and thiol.

In some embodiments, R_2 is heteroaryl optionally substituted with 1, 2, 3, or 4 substituents selected independently from the group consisting of C_{1-6} acyl, C_{2-6} alkenyl, C_{1-6} alkoxy, C_{1-6} alkyl, C_{1-6} alkylcarboxamido, C_{2-6} alkynyl, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonyl, C_{1-6} alkylthio, C_{1-6} alkylureyl, C_{1-6} alkylamino, C_{2-6} dialkylamino, carbo-C_{1-6}-alkoxy, carboxy, cyano, C_{3-6} cycloalkyl, C_{2-6} dialkylcarboxamido, halogen, C_{1-6} haloalkoxy, C_{1-6} haloalkyl, C_{1-6} haloalkylsulfinyl, C_{1-6} haloalkylsulfonyl, hydroxyl, nitro and thiol.

In some embodiments, R_2 is heteroaryl optionally substituted with 1, 2, 3, or 4 substituents selected independently from the group consisting of C_{1-6} acyl, C_{1-6} alkoxy, C_{1-6} alkyl, C_{1-6} alkylamino, C_{2-6} dialkylamino, carbo-C_{1-6}-alkoxy, carboxy, cyano, halogen, C_{1-6} haloalkoxy, C_{1-6} haloalkyl, hydroxyl and nitro.

In some embodiments, R_2 is heteroaryl optionally substituted with 1, 2, 3, or 4 substituents selected independently from the group consisting of C_{1-6} alkoxy, C_{1-6} alkyl, carboxy, cyano, halogen, C_{1-6} haloalkoxy, and C_{1-6} haloalkyl.

In some embodiments, R_2 is heteroaryl optionally substituted with 1, 2, 3, or 4 substituents selected independently from the group consisting of C_{1-6} alkyl, and halogen. In some embodiments, R_2 is heteroaryl optionally substituted with 1, 2, 3, or 4 substituents selected independently from the group consisting of CH_3, F, Cl, and Br.

In some embodiments, the heteroaryl is a 5-member or 6-member heteroaryl, each as described herein, for example as shown in **Tables 2** and **3**.

In some embodiments, R_2 is a 5-member heteroaryl selected from the group consisting of a furanyl, an isoxazolyl, an oxazolyl, an [1,2,4]-oxadiazolyl, an [1,3,4]-oxadiazolyl, a thienyl, an isothiazolyl, a thiazolyl, a [1,2,4]-thiadiazolyl, a [1,3,4-thiadiazolyl, a 1H-pyrrolyl, a 1H-pyrazolyl, an 1H-imidazolyl, a 1H-[1,2,4]-triazolyl, a 1H-[1,2,4]-triazolyl, and a 1H-tetrazolyl.

In some embodiments, R_2 is a 5-member heteroaryl selected from the group consisting of thien-2-yl, thien-3-yl, furan-2-yl and furan-3-yl.

In some embodiments, R_2 is a 6-member heteroaryl selected from the group consisting of a pyridyl, a pyrazine, and a pyrimidinyl.

In some embodiments, R_2 is pyridin-2-yl, pyridin-3-yl, or pyridin-4-yl.

In some embodiments, R_2 is C_{1-6} alkyl optionally substituted with 1, 2, 3, 4 or 5 substituents selected independently from the group consisting of C_{1-6} acyl, acyloxy, C_{2-6} alkenyl, C_{1-6} alkoxy, C_{1-6} alkyl, C_{1-6} alkylcarboxamido, C_{2-6} alkynyl, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonyl, C_{1-6} alkylthio, C_{1-6} alkylureyl, amino, C_{1-6} alkylamino, C_{2-6} dialkylamino, carbo-C_{1-6}-alkoxy,

carboxy, cyano, C_{3-6} cycloalkyl, C_{2-6} dialkylcarboxamido, halogen, C_{1-6} haloalkoxy, C_{1-6} haloalkyl, C_{1-6} haloalkylsulfinyl, C_{1-6} haloalkylsulfonyl, C_{1-6} haloalkylthio, hydroxyl, nitro, and thiol.

In some embodiments, R_2 is C_{1-6} alkyl optionally substituted with 1, 2, 3, 4 or 5 substituents selected independently from the group consisting of C_{1-6} acyl, C_{2-6} alkenyl, C_{1-6} alkoxy, C_{1-6} alkyl, C_{1-6} alkylcarboxamido, C_{2-6} alkynyl, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonyl, C_{1-6} alkylthio, C_{1-6} alkylureyl, C_{1-6} alkylamino, C_{2-6} dialkylamino, carbo-C_{1-6}-alkoxy, carboxy, cyano, C_{3-6} cycloalkyl, C_{2-6} dialkylcarboxamido, halogen, C_{1-6} haloalkoxy, C_{1-6} haloalkyl, C_{1-6} haloalkylsulfinyl, C_{1-6} haloalkylsulfonyl, hydroxyl and nitro.

In some embodiments, R_2 is C_{1-6} alkyl optionally substituted with 1, 2, 3, 4 or 5 substituents selected independently from the group consisting of C_{1-6} acyl, C_{1-6} alkoxy, C_{1-6} alkyl, C_{1-6} alkylamino, C_{2-6} dialkylamino, carbo-C_{1-6}-alkoxy, carboxy, cyano, halogen, C_{1-6} haloalkoxy, C_{1-6} haloalkyl, hydroxyl and nitro.

In some embodiments, R_2 is C_{1-6} alkyl optionally substituted with 1, 2, 3, 4 or 5 substituents selected independently from the group consisting of C_{1-6} alkoxy, C_{1-6} alkyl, carboxy, cyano, halogen, C_{1-6} haloalkoxy, and C_{1-6} haloalkyl.

In some embodiments, R_2 is C_{3-7} cycloalkyl optionally substituted with 1, 2, 3, 4 or 5 substituents selected independently from the group consisting of C_{1-6} alkoxy, C_{1-6} alkyl, carboxy, cyano, halogen, C_{1-6} haloalkoxy, and C_{1-6} haloalkyl.

In some embodiments, R_2 is C_{2-6} alkenyl optionally substituted with 1, 2, 3, 4 or 5 substituents selected independently from the group consisting of C_{1-6} acyl, acyloxy, C_{2-6} alkenyl, C_{1-6} alkoxy, C_{1-6} alkyl, C_{1-6} alkylcarboxamido, C_{2-6} alkynyl, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonyl, C_{1-6} alkylthio, C_{1-6} alkylureyl, amino, C_{1-6} alkylamino, C_{2-6} dialkylamino, carbo-C_{1-6}-alkoxy, carboxy, cyano, C_{3-6} cycloalkyl, C_{2-6} dialkylcarboxamido, halogen, C_{1-6} haloalkoxy, C_{1-6} haloalkyl, C_{1-6} haloalkylsulfinyl, C_{1-6} haloalkylsulfonyl, C_{1-6} haloalkylthio, hydroxyl, nitro and thiol.

In some embodiments, R_2 is C_{2-6} alkenyl optionally substituted with 1, 2, 3, 4 or 5 substituents selected independently from the group consisting of C_{1-6} alkoxy, C_{1-6} alkyl, carboxy, cyano, halogen, C_{1-6} haloalkoxy, and C_{1-6} haloalkyl.

In some embodiments, R_2 is C_{1-6} haloalkyl optionally substituted with 1, 2, 3, 4 or 5 substituents selected independently from the group consisting of C_{1-6} acyl, acyloxy, C_{2-6} alkenyl, C_{1-6} alkoxy, C_{1-6} alkyl, C_{1-6} alkylcarboxamido, C_{2-6} alkynyl, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonyl, C_{1-6} alkylthio, C_{1-6} alkylureyl, amino, C_{1-6} alkylamino, C_{2-6} dialkylamino, carbo-C_{1-6}-alkoxy, carboxy, cyano, C_{3-6} cycloalkyl, C_{2-6} dialkylcarboxamido, halogen, C_{1-6} haloalkoxy, C_{1-6} haloalkylsulfinyl, C_{1-6} haloalkylsulfonyl, C_{1-6} haloalkylthio, hydroxyl, nitro and thiol.

In some embodiments, R_2 is C_{1-6} haloalkyl optionally substituted with 1, 2, 3, 4 or 5 substituents selected independently from the group consisting of C_{1-6} alkoxy, C_{1-6} alkyl, carboxy,

cyano, halogen, and C_{1-6} haloalkoxy.

In some embodiments, A is C_{1-3} alkylene optionally substituted with 1, 2, 3 or 4 substituents selected independently from the group consisting of C_{1-6} alkoxy, C_{1-6} alkyl, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonyl, amino, C_{1-6} alkylamino, C_{2-6} dialkylamino, carbo-C_{1-6}-alkoxy, carboxy, cyano, C_{3-6} cycloalkyl, halogen, C_{1-6} haloalkoxy, C_{1-6} haloalkyl, C_{1-6} haloalkylsulfinyl, C_{1-6} haloalkylsulfonyl, C_{1-6} haloalkylthio and hydroxyl.

In some embodiments, A is C_{1-3} alkylene optionally substituted with 1, 2, 3 or 4 substituents selected independently from the group consisting of C_{1-6} alkoxy, C_{1-6} alkyl, carbo-C_{1-6}-alkoxy, carboxy, cyano, halogen, C_{1-6} haloalkoxy, C_{1-6} haloalkyl and hydroxyl.

In some embodiments, A is C_{1-3} alkylene optionally substituted with 1, 2, 3 or 4 substituents selected independently from the group consisting of C_{1-6} alkoxy, C_{1-6} alkyl, carboxy, cyano, halogen and C_{1-6} haloalkyl.

In some embodiments, A is $-CH_2-$, $-CH(CH_3)-$, $-C(CH_3)_2-$ or $-CH_2CH_2-$.

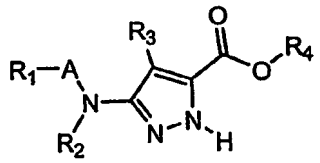
In some embodiments, B is C_{1-3} alkylene optionally substituted with 1, 2, 3 or 4 substituents selected independently from the group consisting of C_{1-6} alkoxy, C_{1-6} alkyl, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonyl, amino, C_{1-6} alkylamino, C_{2-6} dialkylamino, carbo-C_{1-6}-alkoxy, carboxy, cyano, C_{3-6} cycloalkyl, halogen, C_{1-6} haloalkoxy, C_{1-6} haloalkyl, C_{1-6} haloalkylsulfinyl, C_{1-6} haloalkylsulfonyl, C_{1-6} haloalkylthio and hydroxyl.

In some embodiments, B is C_{1-3} alkylene optionally substituted with 1, 2, 3 or 4 substituents selected independently from the group consisting of C_{1-6} alkoxy, C_{1-6} alkyl, carbo-C_{1-6}-alkoxy, carboxy, cyano, halogen, C_{1-6} haloalkoxy, C_{1-6} haloalkyl and hydroxyl.

In some embodiments, B is C_{1-3} alkylene optionally substituted with 1, 2, 3 or 4 substituents selected independently from the group consisting of C_{1-6} alkoxy, C_{1-6} alkyl, carboxy, cyano, halogen and C_{1-6} haloalkyl.

In some embodiments, B is $-CH_2-$, $-CH(CH_3)-$, $-C(CH_3)_2-$ or $-CH_2CH_2-$.

In some embodiments, B is a bond. In this context, B can also be referred to as being absent and it is understood that when B is a bond that R_2 is directly bonded to the nitrogen as illustrated in Formula (Im) below:



(Im)

wherein each variable in Formula (Im) has the same meaning as described herein.

In some embodiments, R_3 is selected from the group consisting of H, C_{1-6} acyl, acyloxy, C_{2-6} alkenyl, C_{1-6} alkoxy, C_{1-6} alkyl, C_{1-6} alkylcarboxamido, C_{2-6} alkynyl, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonyl, C_{1-6} alkylthio, C_{1-6} alkylureyl, amino, C_{1-6} alkylamino, C_{2-6} dialkylamino, carbo-C_{1-6}-alkoxy, cyano, C_{3-6} cycloalkyl, C_{2-6} dialkylcarboxamido, halogen, C_{1-6} haloalkoxy, C_{1-6}

haloalkyl, C_{1-6} haloalkylsulfinyl, C_{1-6} haloalkylsulfonyl, C_{1-6} haloalkylthio, hydroxyl, nitro and thiol.

In some embodiments, R_3 is selected from the group consisting of H, C_{1-6} acyl, acyloxy, C_{2-6} alkenyl, C_{1-6} alkoxy, C_{1-6} alkyl, C_{1-6} alkylcarboxamido, C_{2-6} alkynyl, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonyl, C_{1-6} alkylthio, C_{1-6} alkylureyl, amino, C_{1-6} alkylamino, C_{3-6} dialkylamino, carbo-C_{1-6}-alkoxy, carboxy, cyano, C_{3-6} cycloalkyl, C_{2-6} dialkylcarboxamido, halogen, C_{1-6} haloalkoxy, C_{1-6} haloalkyl, C_{1-6} haloalkylsulfinyl, C_{1-6} haloalkylsulfonyl, C_{1-6} haloalkylthio, hydroxyl, nitro and thiol.

In some embodiments, R_3 is selected from the group consisting of H, C_{1-6} alkoxy, C_{1-6} alkyl, cyano, C_{3-6} cycloalkyl, halogen, C_{1-6} haloalkoxy, C_{1-6} haloalkyl, hydroxyl, nitro and thiol.

In some embodiments, R_3 is selected from the group consisting of H, C_{1-6} alkyl, cyano, halogen, C_{1-6} haloalkyl, hydroxyl and nitro.

In some embodiments, R_3 is selected from the group consisting of H, $-CH_3$, $-CH_2CH_3$, cyano, F, Cl, Br, CF_3 and hydroxyl.

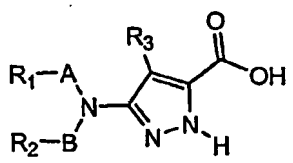
In some embodiments, R_3 is H.

In some embodiments, R_3 is F.

In some embodiments, R_4 is C_{1-6} alkyl. In some embodiments, R_4 is selected from the group consisting of $-CH_3$, $-CH_2CH_3$, $-(CH_2)_2CH_3$, $-(CH_2)_3CH_3$, $-(CH_2)_4CH_3$, $-(CH_2)_5CH_3$, and $-(CH_2)_6CH_3$.

In some embodiments, R_4 is H.

In some embodiments, compounds of the present invention can be represented by Formula (In):



(In)

wherein each variable in Formula (In) has the same meaning as described herein.

In some embodiments:

R_1-A together is benzyl, sec-butyl, 1-methyl-butyl, thiophen-3-ylmethyl, 5-bromo-thiophen-2-ylmethyl, propyl, cyclopropylmethyl, 3-methyl-butyl, 3-methyl-but-2-enyl, cyclohexylmethyl, phenethyl, hexyl, benzo[1,3]dioxol-4-ylmethyl, thiophen-2-ylmethyl, 5-methyl-thiophen-2-ylmethyl, furan-3-ylmethyl, 4-fluoro-benzyl, 3-fluoro-benzyl, or 2-fluoro-benzyl;

R_2-B together is H, benzyl, propyl, cyclopropylmethyl, 3-methyl-butyl, 3-methyl-but-2-enyl, cyclohexylmethyl, phenethyl, hexyl, benzo[1,3]dioxol-4-ylmethyl, thiophen-2-ylmethyl, 5-methyl-thiophen-2-ylmethyl, furan-3-ylmethyl, 5-bromo-thiophen-2-ylmethyl, 4-fluoro-benzyl, 3-

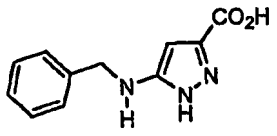
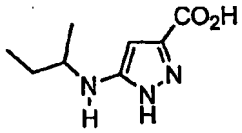
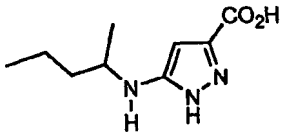
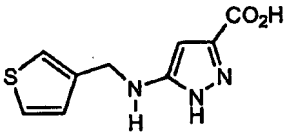
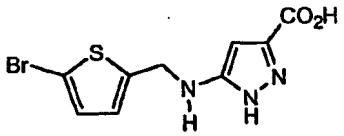
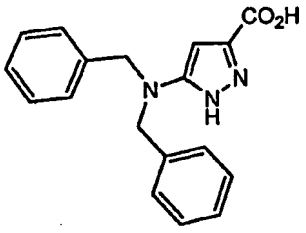
fluoro-benzyl, 2-fluoro-benzyl, or furan-2-ylmethyl;

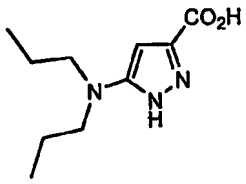
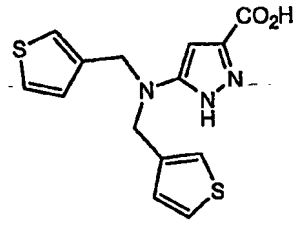
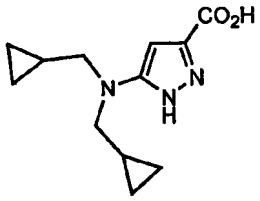
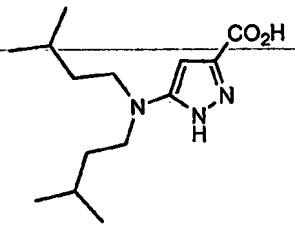
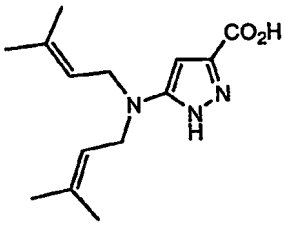
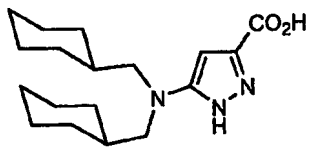
R_3 is H or F; and

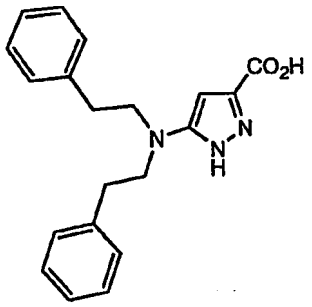
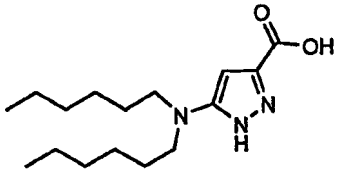
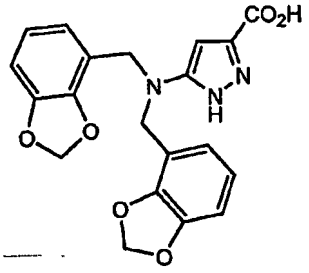
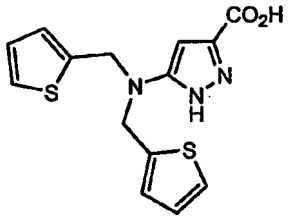
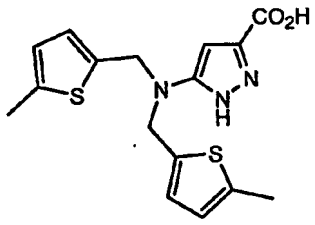
R_4 is H.

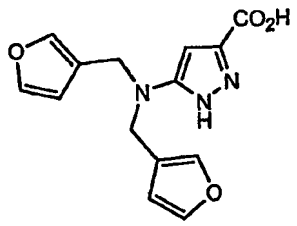
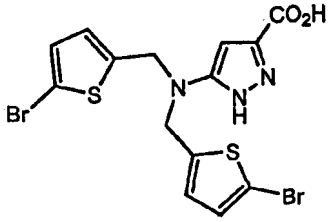
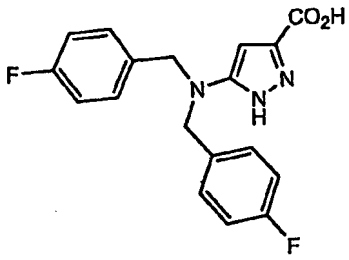
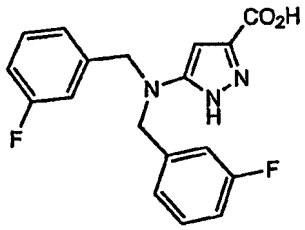
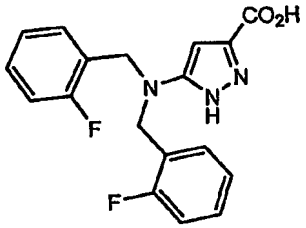
Some embodiments of the present invention include compounds illustrated in TABLE A as shown below.

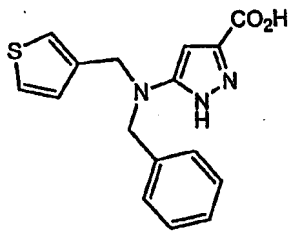
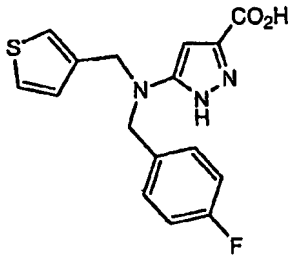
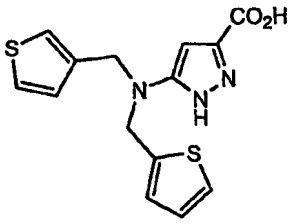
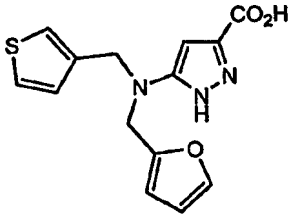
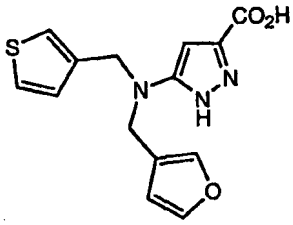
TABLE A

Cmpd#	Chemical Structure	Chemical Name
1		5-Benzylamino-1H-pyrazole-3-carboxylic acid
2		5-sec-Butylamino-1H-pyrazole-3-carboxylic acid
3		5-(1-Methyl-butylamino)-1H-pyrazole-3-carboxylic acid
4		5-[(Thiophen-3-ylmethyl)-amino]-1H-pyrazole-3-carboxylic acid
5		5-[(5-Bromo-thiophen-2-ylmethyl)-amino]-1H-pyrazole-3-carboxylic acid
6		5-Dibenzylamino-1H-pyrazole-3-carboxylic acid

Cmpd#	Chemical Structure	Chemical Name
7		5-Dipropylamino-1H-pyrazole-3-carboxylic acid
8		5-(Bis-thiophen-3-ylmethyl-amino)-1H-pyrazole-3-carboxylic acid
9		5-(Bis-cyclopropylmethyl-amino)-1H-pyrrole-3-carboxylic acid
10		5-[Bis-(3-methyl-butyl)-amino]-1H-pyrrole-3-carboxylic acid
11		5-[Bis-(3-methyl-but-2-enyl)-amino]-1H-pyrrole-3-carboxylic acid
12		5-(Bis-cyclohexylmethyl-amino)-1H-pyrazole-3-carboxylic acid

Cmpd#	Chemical Structure	Chemical Name
13		5-Diphenethylamino-1H-pyrazole-3-carboxylic acid
14		5-Dihexylamino-1H-pyrazole-3-carboxylic acid
15		5-(Bis-benzo[1,3]dioxol-4-ylmethyl-amino)-1H-pyrazole-3-carboxylic acid
16		5-(Bis-thiophen-2-ylmethyl-amino)-1H-pyrazole-3-carboxylic acid
17		5-[Bis-(5-methyl-thiophen-2-ylmethyl)-amino]-1H-pyrazole-3-carboxylic acid

Cmpd#	Chemical Structure	Chemical Name
18		5-(Bis-furan-3-ylmethyl-amino)-1H-pyrazole-3-carboxylic acid
19		5-[Bis-(5-bromo-thiophen-2-ylmethyl)-amino]-1H-pyrazole-3-carboxylic acid
20		5-[Bis-(4-fluoro-benzyl)-amino]-1H-pyrazole-3-carboxylic acid
21		5-[Bis-(3-fluoro-benzyl)-amino]-1H-pyrazole-3-carboxylic acid
22		5-[Bis-(2-fluoro-benzyl)-amino]-1H-pyrazole-3-carboxylic acid

Cmpd#	Chemical Structure	Chemical Name
23		5-(Benzyl-thiophen-3-ylmethyl-amino)-1H-pyrazole-3-carboxylic acid
24		5-[(4-Fluoro-benzyl)-thiophen-3-ylmethyl-amino]-1H-pyrazole-3-carboxylic acid
25		5-(Thiophen-2-ylmethyl-thiophen-3-ylmethyl-amino)-1H-pyrazole-3-carboxylic acid
26		5-(Furan-2-ylmethyl-thiophen-3-ylmethyl-amino)-1H-pyrazole-3-carboxylic acid
27		5-(Furan-3-ylmethyl-thiophen-3-ylmethyl-amino)-1H-pyrazole-3-carboxylic acid

Methods and Uses

Compounds of the present invention can modulate the activity of the **RUP38** receptor. The term "modulate" is meant to refer to the ability to increase or decrease activity of the receptor. In some embodiments, compounds of the invention can be used in methods of modulating a **RUP38** receptor comprising contacting the receptor with an effective amount of any one or more of the compounds as described herein. In still other embodiments, compounds of the invention can be used in methods of modulating a **RUP38** receptor for the treatment of a metabolic-related disorder in an individual in need of such modulation comprising contacting the receptor with a therapeutically-effective amount of a compound of Formula (I). In some embodiments, compounds of the invention increase activity of the **RUP38** receptor. In further embodiments, compounds of the invention are agonists of the **RUP38** receptor. The term "agonist", as used herein, refers to an agent that can stimulate the activity of the receptor (i.e., activate). In some embodiments, compounds of the invention are partial agonists of the **RUP38** receptor.

Some embodiments of the present invention include methods of modulating the **RUP 38** receptor function in a cell, tissue or individual comprising contacting the cell, tissue or individual with an effective amount of a compound of the present invention or a pharmaceutical composition thereof as described herein. In some embodiments, the **RUP 38** receptor function is associated with a metabolic-related disorder.

Another aspect of the present invention pertains to methods of treatment of a metabolic-related disorder comprising administering to an individual in need of such treatment a therapeutically-effective amount of a compound of Formula (I).

Another aspect of the present invention pertains to methods of raising HDL cholesterol levels in an individual comprising administering to the individual a therapeutically-effective amount of a compound of Formula (I).

Another aspect of the present invention pertains to compounds of Formula (I), as described herein, for use in a method of treatment of the human or animal body by therapy.

Another aspect of the present invention pertains to compounds of Formula (I), as described herein, for use in a method of treatment of a metabolic-related disorder of the human or animal body by therapy.

Another aspect of the present invention pertains to compounds of Formula (I), as described herein, for use in a method of treatment of a metabolic-related disorder of the human or animal body by therapy wherein the metabolic-related disorder is selected from the group consisting of dyslipidemia, atherosclerosis, coronary heart disease, insulin resistance, obesity, impaired glucose tolerance, atheromatous disease, hypertension, stroke, Syndrome X, heart disease, type 2 diabetes, hypo-HDL related atherosclerotic risk, ischemic cerebrovascular disease, peripheral vascular disease, stroke, and myocardial infarction.

Another aspect of the present invention pertains to compounds of Formula (I), as described herein, for use in a method of treatment of a metabolic-related disorder of the human or animal body by therapy wherein the metabolic-related disorder is selected from the group consisting of dyslipidemia, atherosclerosis, coronary heart disease, insulin resistance and type 2 diabetes.

Another aspect of the present invention pertains to compounds of Formula (I), as described herein, for use in a method of treatment of atherosclerosis of the human or animal body by therapy.

Another aspect of the present invention pertains to compounds of Formula (I), as described herein, for use in a method of raising HDL cholesterol levels of the human or animal body by therapy.

Another aspect of the present invention pertains to uses of the compounds of Formula (I), as described herein, for the manufacture of a medicament for use in the treatment of a metabolic-related disorder.

Another aspect of the present invention pertains to uses of the compounds of Formula (I), as described herein, for the manufacture of a medicament for use in the treatment of a metabolic-related disorder selected from the group consisting of dyslipidemia, atherosclerosis, coronary heart disease, insulin resistance, obesity, impaired glucose tolerance, atheromatous disease, hypertension, stroke, Syndrome X, heart disease, type 2 diabetes, hypo-HDL related atherosclerotic risk, ischemic cerebrovascular disease, peripheral vascular disease, stroke, and myocardial infarction.

Another aspect of the present invention pertains to uses of the compounds of Formula (I), as described herein, for the manufacture of a medicament for use in the treatment of atherosclerosis.

Another aspect of the present invention pertains to uses of the compounds of Formula (I), as described herein, for the manufacture of a medicament for use in raising HDL cholesterol levels in an individual.

Some embodiments of the present invention relate to methods of treatment of metabolic-related disorders.

In some embodiments the metabolic-related disorder is of the group consisting of dyslipidemia, atherosclerosis, coronary heart disease, insulin resistance, obesity, impaired glucose tolerance, atheromatous disease, hypertension, stroke, Syndrome X, heart disease, type 2 diabetes, hypo-HDL related atherosclerotic risk, ischemic condition such as ischemic cerebrovascular disease, stoke, peripheral vascular disease, stroke, myocardial infarction, and the like.

In some embodiments the metabolic-related disorder is dyslipidemia, atherosclerosis, coronary heart disease, insulin resistance and type 2 diabetes. In some embodiments the metabolic-related disorder is dyslipidemia. In some embodiments the metabolic-related disorder

is atherosclerosis. In some embodiments the metabolic-related disorder is coronary heart disease. In some embodiments the metabolic-related disorder is insulin resistance. In some embodiments the metabolic-related disorder is type 2 diabetes.

In some embodiments related to methods of the present invention, the individual is a mammal. In futher embodiments, the mammal is a human.

Another aspect of the present invention pertains to methods of producing a pharmaceutical composition comprising admixing or combining a compound of Formula (I), as described herein, and a pharmaceutically acceptable carrier.

Pharmaceutical Salts:

The phrase "pharmaceutically acceptable" is employed herein to refer to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgement, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

The present invention also includes pharmaceutically acceptable salts of the compounds described herein. As used herein, "pharmaceutically acceptable salts" refers to derivatives of the disclosed compounds wherein the parent compound is modified by converting an existing acid or base moiety to its salt form. Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic residues such as amines; alkali or organic salts of acidic residues such as carboxylic acids; and the like. The pharmaceutically acceptable salts of the present invention include the conventional non-toxic salts or the quaternary ammonium salts of the parent compound formed, for example, from non-toxic inorganic or organic acids. The pharmaceutically acceptable salts of the present invention can be synthesized from the parent compound which contains a basic or acidic moiety by conventional chemical methods. Generally, such salts can be prepared by reacting the free acid or base forms of these compounds with a stoichiometric amount of the appropriate base or acid in water or in an organic solvent, or in a mixture of the two; generally, nonaqueous media like ether, ethyl acetate, ethanol, isopropanol, or acetonitrile are preferred. Lists of suitable salts are found in *Remington's Pharmaceutical Sciences*, 17th ed., Mack Publishing Company, Easton, Pa., 1985, p. 1418 and *Journal of Pharmaceutical Science*, 66, 2 (1977), each of which is incorporated herein by reference in its entirety.

The present invention also includes prodrugs of the compounds described herein. As used herein, "prodrugs" refer to any covalently bonded carriers which release the active parent drug when administered to a mammalian subject. Prodrugs can be prepared by modifying functional groups present in the compounds in such a way that the modifications are cleaved, either in routine manipulation or *in vivo*, to the parent compounds. Prodrugs include compounds wherein hydroxyl, amino, sulfhydryl, or carboxyl groups are bonded to any group that, when administered

to a mammalian subject, cleaves to form a free hydroxyl, amino, sulfhydryl, or carboxyl group respectively. Examples of prodrugs include, but are not limited to, acetate, formate and benzoate derivatives of alcohol and amine functional groups in the compounds of the invention. Preparation and use of prodrugs is discussed in T. Higuchi and V. Stella, "Pro-drugs as Novel Delivery Systems," Vol. 14 of the A.C.S. Symposium Series, and in *Bioreversible Carriers in Drug Design*, ed. Edward B. Roche, American Pharmaceutical Association and Pergamon Press, 1987, both of which are hereby incorporated by reference in their entirety.

Combination Therapy:

While the compounds of the invention can be administered as the sole active pharmaceutical agent (i.e., mono-therapy), compounds of the invention can also be used in combination with other pharmaceutical agents (i.e., combination-therapy) for the treatment of the diseases/conditions/disorders described herein. Therefore, another aspect of the present invention includes methods of treatment comprising administering to an individual in need of treatment a therapeutically effective amount of a compound of the present invention, for example Formula (I), in combination with one or more additional pharmaceutical agent as described herein.

Suitable pharmaceutical agents that can be used in combination with the compounds of the present invention include anti-obesity agents such as apolipoprotein-B secretion/microsomal triglyceride transfer protein (apo-B/MTP) inhibitors, MCR-4 agonists, cholescystokinin-A (CCK-A) agonists, serotonin and norepinephrine reuptake inhibitors (for example, sibutramine), sympathomimetic agensts, β_3 adrenergic receptor agonists, dopamine agonists (for example, bromocriptine), melanocyte-stimulating hormone receptor analogs, cannabinoid 1 receptor antagonists [for example, SR141716: *N*-(piperidin-1-yl)-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1*H*-pyrazole-3-carboxamide], melanin concentrating hormone antagonists, leptons (the OB protein), leptin analogues, leptin receptor agonists, galanin antagonists, lipase inhibitors (such as tetrahydrolipstatin, i.e., Orlistat), anorectic agents (such as a bombesin agonist), Neuropeptide-Y antagonists, thyromimetic agents, dehydroepiandrosterone or an analogue thereof, glucocorticoid receptor agonists or antagonists, orexin receptor antagonists, urocortin binding protein antagonists, glucagon-like peptide-1 receptor agonists, ciliary neutrotrophic factors (such as Axokine™ available from Regeneron Pharmaceuticals, Inc., Tarrytown, NY and Procter & Gamble Company, Cincinnati, OH), human agouti-related proteins (AGRP), ghrelin receptor antagonists, histamine 3 receptor antagonists or reverse agonists, neuromedin U receptor agonists, noradrenergic anorectic agents (for example, phentermine, mazindol and the like) and appetite suppressants (for example, bupropion).

Other anti-obesity agents, including the agents set forth *infra*, are well known, or will be readily apparent in light of the instant disclosure, to one of ordinary skill in the art.

In some embodiments, the anti-obesity agents are selected from the group consisting of

orlistat, sibutramine, bromocriptine, ephedrine, leptin, and pseudoephedrine. In a further embodiment, compounds of the present invention and combination therapies are administered in conjunction with exercise and/or a sensible diet.

It will be understood that the scope of combination-therapy of the compounds of the present invention with other anti-obesity agents, anorectic agents, appetite suppressant and related agents is not limited to those listed above, but includes in principle any combination with any pharmaceutical agent or pharmaceutical composition useful for the treatment of overweight and obese individuals.

Other suitable pharmaceutical agents, in addition to anti-obesity agents, that can be used in combination with the compounds of the present invention include agents useful in the treatment of concomitant diseases. For example, individuals that are over weight or obese increase their risk of morbidity and mortality arising from concomitant diseases, such as, metabolic-related disorders including congestive heart failure, type 2 diabetes, atherosclerosis, dyslipidemia, hyperinsulinemia, hypertension, insulin resistance, hyperglycemia, retinopathy, nephropathy, neuropathy, and the like. Treatment for one or more of the diseases cited herein include the use of one or more pharmaceutical agents known in the art belonging to the classes of drugs referred to, but not limited to, the following: sulfonylureas, meglitinides, biguanides, α-glucosidase inhibitors, peroxisome proliferators-activated receptor-γ (i.e., PPAR-γ) agonists, insulin, insulin analogues, HMG-CoA reductase inhibitors, cholesterol-lowering drugs (for example, fibrates that include: fenofibrate, bezafibrate, gemfibrozil, clofibrate and the like; bile acid sequestrants which include: cholestyramine, colestipol and the like; and niacin), antiplatelet agents (for example, aspirin and adenosine diphosphate receptor antagonists that include: clopidogrel, ticlopidine and the like), angiotensin-converting enzyme inhibitors, angiotensin II receptor antagonists, adiponectin, agonists for the adiponectin receptor (AdipoR1 and/or AdipoR2), and DP receptor antagonists. In accordance to one aspect of the present invention, a compound of the present can be used in combination with a pharmaceutical agent or agents belonging to one or more of the classes of drugs cited herein.

It will be understood that the scope of combination-therapy of the compounds of the present invention with other pharmaceutical agents is not limited to those listed herein, *supra* or *infra*, but includes in principle any combination with any pharmaceutical agent or pharmaceutical composition useful for the treatment diseases, conditions or disorders that are linked to overweight and obese individuals.

Some embodiments of the present invention include methods of treatment of a disease, disorder or condition as described herein comprising administering to an individual in need of such treatment a therapeutically effect amount or dose of a compound of the present invention in combination with at least one pharmaceutical agent selected from the group consisting of: sulfonylureas, meglitinides, biguanides, α-glucosidase inhibitors, peroxisome proliferators-

activated receptor-γ (i.e., PPAR-γ) agonists; insulin, insulin analogues, HMG-CoA reductase inhibitors, cholesterol-lowering drugs (for example, fibrates that include: fenofibrate, bezafibrate, gemfibrozil, clofibrate and the like; bile acid sequestrants which include: cholestyramine, colestipol and the like; and niacin), antiplatelet agents (for example, aspirin and adenosine diphosphate receptor antagonists that include: clopidogrel, ticlopidine and the like), angiotensin-converting enzyme inhibitors, angiotensin II receptor antagonists and adiponectin and agonists for the adiponectin receptor (AdipoR1 and/or AdipoR2). In some embodiments, methods of the present invention include compounds of the present invention and the pharmaceutical agents are administered separately. In further embodiments, compounds of the present invention and the pharmaceutical agents are administered together.

Suitable pharmaceutical agents that can be used in conjunction with compounds of the present invention include α-glucosidase inhibitors. α-Glucosidase inhibitors belong to the class of drugs which competitively inhibit digestive enzymes such as α-amylase, maltase, α-dextrinase, sucrase, etc. in the pancreas and or small intesting. The reversible inhibition by α-glucosidase inhibitors retard, diminish or otherwise reduce blood glucose levels by delaying the digestion of starch and sugars. Some representative examples of α-glucosidase inhibitors include acarbose, N-(1,3-dihydroxy-2-propyl)valiolamine (generic name; voglibose), miglitol, and α-glucosidase inhibitors known in the art.

Suitable pharmaceutical agents that can be used in conjunction with compounds of the present invention include sulfonylureas. The sulfonylureas (SU) are drugs which promote secretion of insulin from pancreatic β cells by transmitting signals of insulin secretion via SU receptors in the cell membranes. Examples of the sulfonylureas include glyburide, glipizide, glimepiride and other sulfonylureas known in the art.

Suitable pharmaceutical agents that can be used in conjunction with compounds of the present invention include the meglitinides. The meglitinides are benzoic acid derivatives represent a novel class of insulin secretagogues. These agents target postprandial hyperglycemia and show comparable efficacy to sulfonylureas in reducing HbA_{1c}. Examples of meglitinides include repaglinide, nateglinide and other meglitinides known in the art.

Suitable pharmaceutical agents that can be used in conjunction with compounds of the present invention include the biguanides. The biguanides represent a class of drugs that stimulate anaerobic glycolysis, increase the sensitivity to insulin in the peripheral tissues, inhibit glucose absorption from the intestine, suppress of hepatic gluconeogenesis, and inhibit fatty acid oxidation. Examples of biguanides include phenformin, metformin, buformin, and biguanides known in the art.

Suitable pharmaceutical agents that can be used in conjunction with compounds of the present invention include the α-glucosidase inhibitors. The α-glucosidase inhibitors competitively inhibit digestive enzymes such as α-amylase, maltase, α-dextrinase, sucrase, etc. in

the pancreas and or small intestine. The reversible inhibition by α-glucosidase inhibitors retard, diminish or otherwise reduce blood glucose levels by delaying the digestion of starch and sugars. Examples of α-glucosidase inhibitors include acarbose, N-(1,3-dihydroxy-2-propyl)valiolamine (generic name; voglibose), miglitol, and α-glucosidase inhibitors known in the art.

Suitable pharmaceutical agents that can be used in conjunction with compounds of the present invention include the peroxisome proliferators-activated receptor-γ (i.e., PPAR-γ) agonists. The peroxisome proliferators-activated receptor-γ agonists represent a class of compounds that activates the nuclear receptor PPAR-γ and therefore regulate the transcription of insulin-responsive genes involved in the control of glucose production, transport and utilization. Agents in the class also facilitate the regulation of fatty acid metabolism. Examples of PPAR-γ agonists include rosiglitazone, pioglitazone, tesaglitazar, netoglitazone, GW-409544, GW-501516 and PPAR-γ agonists known in the art.

Suitable pharmaceutical agents that can be used in conjunction with compounds of the present invention include the HMG-CoA reductase inhibitors. The HMG-CoA reductase inhibitors are agents also referred to as Statin compounds that belong to a class of drugs that lower blood cholesterol levels by inhibiting hydroxymethylglutalyl CoA (HMG-CoA) reductase. HMG-CoA reductase is the rate-limiting enzyme in cholesterol biosynthesis. The statins lower serum LDL concentrations by upregulating the activity of LDL receptors and are responsible for clearing LDL from the blood. Some representative examples the statin compounds include rosuvastatin, pravastatin and its sodium salt, simvastatin, lovastatin, atorvastatin, fluvastatin, cerivastatin, rosuvastatin, pitavastatin, BMS's "superstatin", and HMG-CoA reductase inhibitors known in the art.

Suitable pharmaceutical agents that can be used in conjunction with compounds of the present invention include the angiotensin converting enzyme (ACE) inhibitors. The angiotensin converting enzyme inhibitors belong to the class of drugs that partially lower blood glucose levels as well as lowering blood pressure by inhibiting angiotensin converting enzymes. Examples of the angiotensin converting enzyme inhibitors include captopril, enalapril, alacepril, delapril; ramipril, lisinopril, imidapril, benazepril, ceronapril, cilazapril, enalaprilat, fosinopril, moveltopril, perindopril, quinapril, spirapril, temocapril, trandolapril, and angiotensin converting enzyme inhibitors known in the art.

Suitable pharmaceutical agents that can be used in conjunction with compounds of the present invention include the angiotensin II receptor antagonists. Angiotensin II receptor antagonists target the angiotensin II receptor subtype 1 (i.e., AT1) and demonstrate a beneficial effect on hypertension. Examples of angiotensin II receptor antagonists include losartan (and the potassium salt form), and angiotensin II receptor antagonists known in the art.

Suitable pharmaceutical agents that can be used in conjunction with compounds of the present invention include DP receptor antagonists. DP receptor antagonists include those

described in WO01/79169, EP03/062200, WO01/66520, WO03/022814, WO03/078409, WO2004/103370, and like antagonists.

Other treatments for one or more of the diseases cited herein include the use of pharmaceutical agents known in the art belonging to the classes of drugs referred to, but not limited to, the following: amylin agonists (for example, pramlintide), insulin secretagogues (for example, GLP-1 agonists; exendin-4; insulinotropin (NN2211); dipeptyl peptidase inhibitors (for example, NVP-DPP-728), acyl CoA cholesterol acetyltransferase inhibitors (for example, Ezetimibe, eflucimibe, and like compounds), cholesterol absorption inhibitors (for example, ezetimibe, pamaqueside and like compounds), cholesterol ester transfer protein inhibitors (for example, CP-529414, JTT-705, CETi-1, and like compounds), microsomal triglyceride transfer protein inhibitors (for example, implitapide, and like compounds), cholesterol modulators (for example, NO-1886, and like compounds), bile acid modulators (for example, GT103-279 and like compounds) and squalene synthase inhibitors.

Squalene synthesis inhibitors belong to a class of drugs that lower blood cholesterol levels by inhibiting synthesis of squalene. Examples of the squalene synthesis inhibitors include (S)-α-[Bis[2,2-dimethyl-1-oxopropoxy)methoxy] phosphinyl]-3-phenoxybenzenebutanesulfonic acid, mono potassium salt (BMS-188494) and squalene synthesis inhibitors known in the art.

Compositions of the Present Invention

According to a further aspect, the present invention also pertains to pharmaceutical compositions comprising one or more compounds of Formula (I) or any formulae disclosed herein, and one or more pharmaceutically acceptable carriers.

Some embodiments of the present invention include a method of producing a pharmaceutical composition comprising admixing at least one compound according to any of the compound embodiments disclosed herein and a pharmaceutically acceptable carrier. Formulations may be prepared by any suitable method, typically by uniformly mixing the active compound(s) with liquids or finely divided solid carriers, or both, in the required proportions, and then, if necessary, forming the resulting mixture into a desired shape.

Conventional excipients, such as binding agents, fillers, acceptable wetting agents, tabletting lubricants, and disintegrants may be used in tablets and capsules for oral administration. Liquid preparations for oral administration may be in the form of solutions, emulsions, aqueous or oily suspensions, and syrups. Alternatively, the oral preparations may be in the form of dry powder that can be reconstituted with water or another suitable liquid vehicle before use. Additional additives such as suspending or emulsifying agents, non-aqueous vehicles (including edible oils), preservatives, and flavorings and colorants may be added to the liquid preparations. Parenteral dosage forms may be prepared by dissolving the compound of the invention in a suitable liquid vehicle and filter sterilizing the solution before filling and sealing an appropriate

vial or ampoule. These are just a few examples of the many appropriate methods well known in the art for preparing dosage forms.

A compound of the present invention can be formulated into pharmaceutical compositions using techniques well known to those in the art. Suitable pharmaceutically-acceptable carriers, outside those mentioned herein, are known in the art; for example, see Remington, The Science and Practice of Pharmacy, 20th Edition, 2000, Lippincott Williams & Wilkins, (Editors: Gennaro, A. R., et al.).

While it is possible that, for use in the treatment, a compound of the invention may, in an alternative use, be administered as a raw or pure chemical, it is preferable however to present the compound or active ingredient as a pharmaceutical formulation or composition further comprising a pharmaceutically acceptable carrier.

The invention thus further provides pharmaceutical formulations comprising a compound of the invention or a pharmaceutically acceptable salt thereof together with one or more pharmaceutically acceptable carriers thereof. The carrier(s) must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not overly deleterious to the recipient thereof.

Pharmaceutical formulations include those suitable for oral, rectal, nasal, topical (including buccal and sub-lingual), vaginal or parenteral (including intramuscular, sub-cutaneous and intravenous) administration or in a form suitable for administration by inhalation, insufflation or by a transdermal patch. Transdermal patches dispense a drug at a controlled rate by presenting the drug for absorption in an efficient manner with a minimum of degradation of the drug. Typically, transdermal patches comprise an impermeable backing layer, a single pressure sensitive adhesive and a removable protective layer with a release liner. One of ordinary skill in the art will understand and appreciate the techniques appropriate for manufacturing a desired efficacious transdermal patch based upon the needs of the artisan.

The compounds of the invention, together with a conventional adjuvant, carrier, or diluent, may thus be placed into the form of pharmaceutical formulations and unit dosages thereof, and in such form may be employed as solids, such as tablets or filled capsules, or liquids such as solutions, suspensions, emulsions, elixirs, gels or capsules filled with the same, all for oral use, in the form of suppositories for rectal administration; or in the form of sterile injectable solutions for parenteral (including subcutaneous) use. Such pharmaceutical compositions and unit dosage forms thereof may comprise conventional ingredients in conventional proportions, with or without additional active compounds or principles, and such unit dosage forms may contain any suitable effective amount of the active ingredient commensurate with the intended daily dosage range to be employed.

For oral administration, the pharmaceutical composition may be in the form of, for example, a tablet, capsule, suspension or liquid. The pharmaceutical composition is preferably

made in the form of a dosage unit containing a particular amount of the active ingredient. Examples of such dosage units are capsules, tablets, powders, granules or a suspension, with conventional additives such as lactose, mannitol, corn starch or potato starch; with binders such as crystalline cellulose, cellulose derivatives, acacia, corn starch or gelatins; with disintegrators such as corn starch, potato starch or sodium carboxymethyl-cellulose; and with lubricants such as talc or magnesium stearate. The active ingredient may also be administered by injection as a composition wherein, for example, saline, dextrose or water may be used as a suitable pharmaceutically acceptable carrier.

Compounds of the present invention or a physiologically functional derivative thereof can be used as active ingredients in pharmaceutical compositions, specifically as RUP38 receptor modulators. The term "active ingredient" is defined in the context of a "pharmaceutical composition" and shall mean a component of a pharmaceutical composition that provides the primary pharmacological effect, as opposed to an "inactive ingredient" which would generally be recognized as providing no pharmaceutical benefit.

The dose when using the compounds of the present invention can vary within wide limits, and as is customary and is known to the physician, it is to be tailored to the individual conditions in each individual case. It depends, for example, on the nature and severity of the illness to be treated, on the condition of the patient, on the compound employed or on whether an acute or chronic disease state is treated or on whether further active compounds are administered in addition to the compounds of the present invention. Representative doses of the present invention include, but not limited to, about 0.001 mg to about 5000 mg, about 0.001 to about 2500 mg, about 0.001 to about 1000 mg, 0.001 to about 500 mg, 0.001 mg to about 250 mg, about 0.001 mg to 100 mg, about 0.001 mg to about 50 mg, and about 0.001 mg to about 25 mg. Multiple doses may be administered during the day, especially when relatively large amounts are deemed to be needed, for example 2, 3 or 4, doses. Depending on the individual and as deemed appropriate from the patient's physician or care-giver it may be necessary to deviate upward or downward from the doses described herein.

The amount of active ingredient, or an active salt or derivative thereof, required for use in treatment will vary not only with the particular salt selected but also with the route of administration, the nature of the condition being treated and the age and condition of the patient and will ultimately be at the discretion of the attendant physician or clinician. In general, one skilled in the art understands how to extrapolate in vivo data obtained in a model system, typically an animal model, to another, such as a human. Typically, animal models include, but are not limited to, the rodents. In some circumstances, these extrapolations may merely be based on the weight of the animal in the respective model in comparison to another, such as a mammal, preferably a human, however, more often, these extrapolations are not simply based on weights, but rather incorporate a variety of factors. Representative factors include, but not limited to, the

type, age, weight, sex, diet and medical condition of the patient, the severity of the disease, the route of administration, pharmacological considerations such as the activity, efficacy, pharmacokinetic and toxicology profiles of the particular compound employed, whether a drug delivery system is utilized, on whether an acute or chronic disease state is being treated or on whether further active compounds are administered in addition to the compounds of the Formula (I) and as part of a drug combination. The dosage regimen for treating a disease condition with the compounds and/or compositions of this invention is selected in accordance with a variety factors as cited above. Thus, the actual dosage regimen employed may vary widely and therefore may deviate from a preferred dosage regimen and one skilled in the art will recognize that dosage and dosage regimen outside these typical ranges can be tested and, where appropriate, may be used in the methods of this invention.

The desired dose may conveniently be presented in a single dose or as divided doses administered at appropriate intervals, for example, as two, three, four or more sub-doses per day. The sub-dose itself may be further divided, e.g., into a number of discrete loosely spaced administrations. The daily dose can be divided, especially when relatively large amounts are administered as deemed appropriate, into several, for example 2, 3 or 4, part administrations. If appropriate, depending on individual behavior, it may be necessary to deviate upward or downward from the daily dose indicated.

The compounds of the present invention can be administrated in a wide variety of oral and parenteral dosage forms. It will be obvious to those skilled in the art that the following dosage forms may comprise, as the active component, either a compound of the invention or a pharmaceutically acceptable salt of a compound of the invention.

For preparing pharmaceutical compositions from the compounds of the present invention, the selection of a suitable pharmaceutically acceptable carrier can be either solid, liquid or a mixture of both. Solid form preparations include powders, tablets, pills, capsules, cachets, suppositories, and dispersible granules. A solid carrier can be one or more substances which may also act as diluents, flavouring agents, solubilizers, lubricants, suspending agents, binders, preservatives, tablet disintegrating agents, or an encapsulating material.

In powders, the carrier is a finely divided solid which is in a mixture with the finely divided active component.

In tablets, the active component is mixed with the carrier having the necessary binding capacity in suitable proportions and compacted to the desire shape and size.

The powders and tablets may contain varying percentage amounts of the active compound. A representative amount in a powder or tablet may contain from 0.5 to about 90 percent of the active compound; however, an artisan would know when amounts outside of this range are necessary. Suitable carriers for powders and tablets are magnesium carbonate, magnesium stearate, talc, sugar, lactose, pectin, dextrin, starch, gelatin, tragacanth,

methylcellulose, sodium carboxymethylcellulose, a low melting wax, cocoa butter, and the like. The term "preparation" is intended to include the formulation of the active compound with encapsulating material as carrier providing a capsule in which the active component, with or without carriers, is surrounded by a carrier, which is thus in association with it. Similarly, cachets and lozenges are included. Tablets, powders, capsules, pills, cachets, and lozenges can be used as solid forms suitable for oral administration.

For preparing suppositories, a low melting wax, such as an admixture of fatty acid glycerides or cocoa butter, is first melted and the active component is dispersed homogeneously therein, as by stirring. The molten homogenous mixture is then poured into convenient sized molds, allowed to cool, and thereby to solidify.

Formulations suitable for vaginal administration may be presented as pessaries, tampons, creams, gels, pastes, foams or sprays containing in addition to the active ingredient such carriers as are known in the art to be appropriate.

Liquid form preparations include solutions, suspensions, and emulsions, for example, water or water-propylene glycol solutions. For example, parenteral injection liquid preparations can be formulated as solutions in aqueous polyethylene glycol solution. Injectable preparations, for example, sterile injectable aqueous or oleaginous suspensions may be formulated according to the known art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution or suspension in a nontoxic parenterally acceptable diluent or solvent, for example, as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution, and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

The compounds according to the present invention may thus be formulated for parenteral administration (e.g. by injection, for example bolus injection or continuous infusion) and may be presented in unit dose form in ampoules, pre-filled syringes, small volume infusion or in multi-dose containers with an added preservative. The pharmaceutical compositions may take such forms as suspensions, solutions, or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilizing and/or dispersing agents. Alternatively, the active ingredient may be in powder form, obtained by aseptic isolation of sterile solid or by lyophilization from solution, for constitution with a suitable vehicle, e.g. sterile, pyrogen-free water, before use.

Aqueous formulations suitable for oral use can be prepared by dissolving or suspending the active component in water and adding suitable colorants, flavours, stabilizing and thickening agents, as desired.

Aqueous suspensions suitable for oral use can be made by dispersing the finely divided active component in water with viscous material, such as natural or synthetic gums, resins, methylcellulose, sodium carboxymethylcellulose, or other well known suspending agents.

Also included are solid form preparations which are intended to be converted, shortly before use, to liquid form preparations for oral administration. Such liquid forms include solutions, suspensions, and emulsions. These preparations may contain, in addition to the active component, colorants, flavors, stabilizers, buffers, artificial and natural sweeteners, dispersants, thickeners, solubilizing agents, and the like.

For topical administration to the epidermis the compounds according to the invention may be formulated as ointments, creams or lotions, or as a transdermal patch.

Ointments and creams may, for example, be formulated with an aqueous or oily base with the addition of suitable thickening and/or gelling agents. Lotions may be formulated with an aqueous or oily base and will in general also contain one or more emulsifying agents, stabilizing agents, dispersing agents, suspending agents, thickening agents, or coloring agents.

Formulations suitable for topical administration in the mouth include lozenges comprising active agent in a flavored base, usually sucrose and acacia or tragacanth; pastilles comprising the active ingredient in an inert base such as gelatin and glycerin or sucrose and acacia; and mouthwashes comprising the active ingredient in a suitable liquid carrier.

Solutions or suspensions are applied directly to the nasal cavity by conventional means, for example with a dropper, pipette or spray. The formulations may be provided in single or multi-dose form. In the latter case of a dropper or pipette, this may be achieved by the patient administering an appropriate, predetermined volume of the solution or suspension. In the case of a spray, this may be achieved for example by means of a metering atomizing spray pump.

Administration to the respiratory tract may also be achieved by means of an aerosol formulation in which the active ingredient is provided in a pressurized pack with a suitable propellant. If the compounds of the Formula (I) or pharmaceutical compositions comprising them are administered as aerosols, for example as nasal aerosols or by inhalation, this can be carried out, for example, using a spray, a nebulizer, a pump nebulizer, an inhalation apparatus, a metered inhaler or a dry powder inhaler. Pharmaceutical forms for administration of the compounds of the Formula (I) as an aerosol can be prepared by processes well-known to the person skilled in the art. For their preparation, for example, solutions or dispersions of the compounds of the Formula (I) in water, water/alcohol mixtures or suitable saline solutions can be employed using customary additives, for example benzyl alcohol or other suitable preservatives, absorption enhancers for increasing the bioavailability, solubilizers, dispersants and others, and, if appropriate, customary propellants, for example include carbon dioxide, CFC's, such as, dichlorodifluoromethane, trichlorofluoromethane, or dichlorotetrafluoroethane; and the like. The aerosol may conveniently also contain a surfactant such as lecithin. The dose of drug may be controlled by provision of a

metered valve.

In formulations intended for administration to the respiratory tract, including intranasal formulations, the compound will generally have a small particle size for example of the order of 10 microns or less. Such a particle size may be obtained by means known in the art, for example by micronization. When desired, formulations adapted to give sustained release of the active ingredient may be employed.

Alternatively the active ingredients may be provided in the form of a dry powder, for example, a powder mix of the compound in a suitable powder base such as lactose, starch, starch derivatives such as hydroxypropylmethyl cellulose and polyvinylpyrrolidone (PVP). Conveniently the powder carrier will form a gel in the nasal cavity. The powder composition may be presented in unit dose form for example in capsules or cartridges of, e.g., gelatin, or blister packs from which the powder may be administered by means of an inhaler.

The pharmaceutical preparations are preferably in unit dosage forms. In such form, the preparation is subdivided into unit doses containing appropriate quantities of the active component. The unit dosage form can be a packaged preparation, the package containing discrete quantities of preparation, such as packeted tablets, capsules, and powders in vials or ampoules. Also, the unit dosage form can be a capsule, tablet, cachet, or lozenge itself, or it can be the appropriate number of any of these in packaged form.

Tablets or capsules for oral administration and liquids for intravenous administration are preferred compositions.

Some embodiments of the present invention include a method of producing a pharmaceutical composition for "combination-therapy" comprising admixing at least one compound according to any of the compound embodiments disclosed herein, together with at least one known pharmaceutical agent as described herein and a pharmaceutically acceptable carrier.

Chemistry and Methods of Preparation of Compounds of the Invention:

Compounds of the invention, including salts thereof, can be prepared using known organic synthesis techniques and can be synthesized according to any of the numerous possible synthetic routes.

The compounds described herein can be asymmetric (e.g., having one or more stereocenters). All stereoisomers, such as enantiomers and diastereomers, are intended unless otherwise indicated. Compounds of the present invention that contain asymmetrically substituted carbon atoms can be isolated in optically active or racemic forms. Methods on how to prepare optically active forms from optically active starting materials are known in the art, such as by resolution of racemic mixtures or by stereoselective synthesis. Many geometric isomers of, such as, olefins, and the like can also be present in the compounds described herein, and all such stable isomers are contemplated in the present invention. Cis and trans geometric isomers of the

compounds of the present invention are described and may be isolated as a mixture of isomers or as separated isomeric forms.

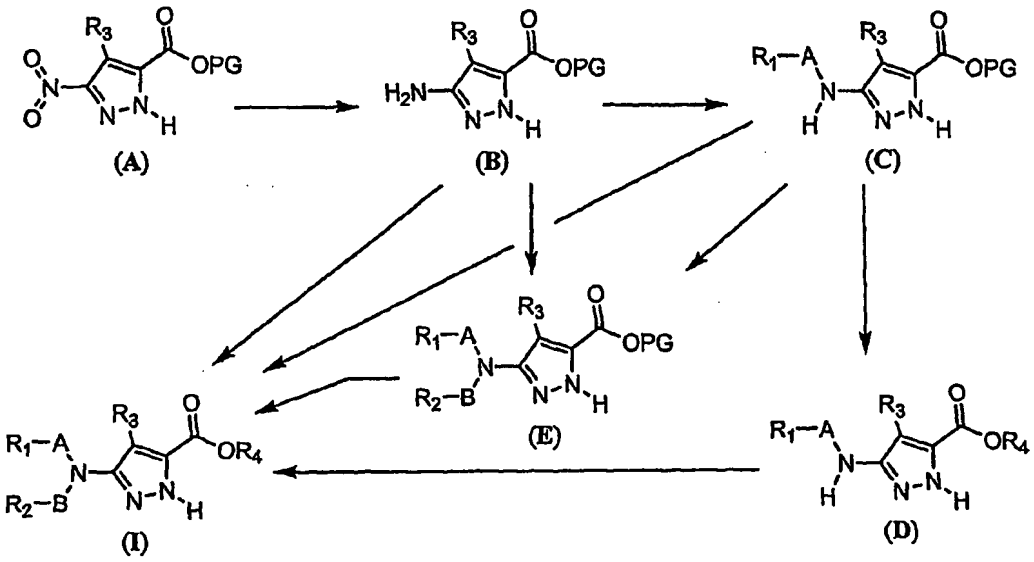
Resolution of racemic mixtures of compounds can be carried out by any of the numerous methods known in the art. Suitable resolving agents for fractional recrystallization methods are, for example, optically active acids, such as the D and L forms of tartaric acid, diacetyltartaric acid, dibenzoyltartaric acid, mandelic acid, malic acid, lactic acid or the various optically active camphorsulfonic acids such as β-camphorsulfonic acid. Other resolving agents suitable for fractional crystallization methods include stereoisomerically pure forms of α-methylbenzylamine (e.g., *S* and *R* forms, or diastereomerically pure forms), 2-phenylglycinol, norephedrine, ephedrine, N-methylephedrine, cyclohexylethylamine, 1,2-diaminocyclohexane, and the like. Resolution of racemic mixtures can also be carried out by elution on a column packed with an optically active resolving agent (e.g., dinitrobenzoylphenylglycine). Suitable elution solvent composition can be determined by one skilled in the art.

The reactions for preparing compounds of the invention can be carried out in suitable solvents which can be readily selected by one of skill in the art of organic synthesis. Suitable solvents can be substantially nonreactive with the starting materials (reactants), the intermediates, or products at the temperatures at which the reactions are carried out, i.e., temperatures which can range from the solvent's freezing temperature to the solvent's boiling temperature. A given reaction can be carried out in one solvent or a mixture of more than one solvent. Depending on the particular reaction step, suitable solvents for a particular reaction step can be selected.

Compounds of the invention can be generally prepared by the methods illustrated below, according to Schemes I through II. The symbols in the formulae shown in Schemes I and II have the same definitions as used throughout this disclosure.

One representative synthesis is set forth below in Scheme I:

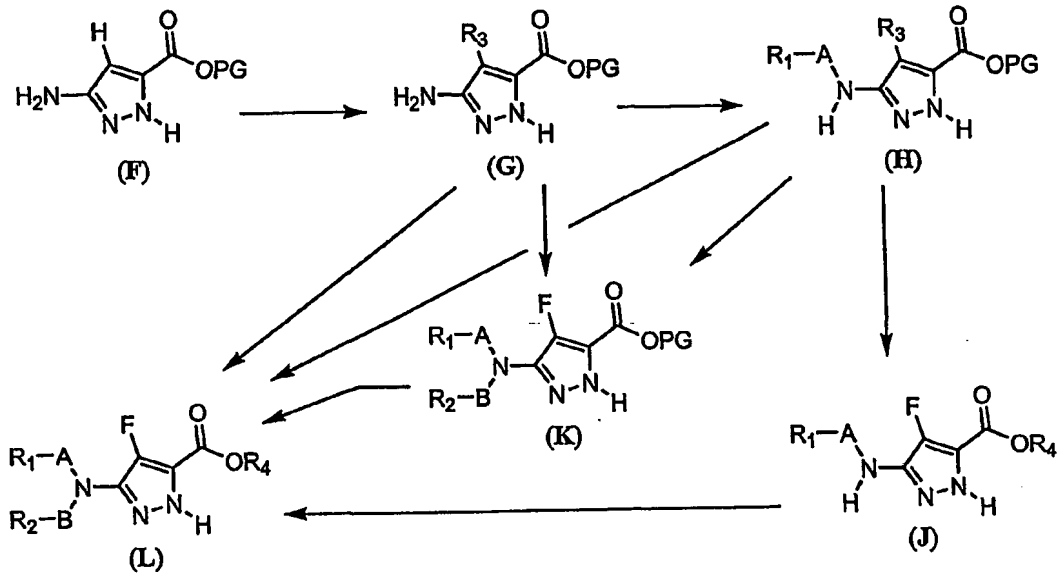
Scheme I



By utilizing, for example, appropriately substituted nitro-pyrazoles of Formula (A) having any of a wide variety for substituents for R_3 and the protecting group "PG", the corresponding amino-pyrazoles of Formula (B) can be prepared via reduction of the nitro group. In some embodiments, "PG" is a C_{1-6} alkyl group. In a subsequent step, amino-pyrazoles of Formula (B) can be converted to mono-*N*-substituted aminopyrazoles of Formula (C) via a reductive amination. This step involves two aspects, 1) the formation of an intermediate imine and 2) reduction of the imine to mono-*N*-substituted aminopyrazoles of Formula (C). The formation of the imine and reduction can be conducted as one step without isolation of the imine or the reduction can be conducted with an isolated imine as a separate step. A variety of aldehydes and ketones can be used in this step providing a wide variety of R_1-A- groups. Mono-*N*-substituted aminopyrazoles of Formula (C) can be converted to compounds of the invention, wherein R_2-B- is hydrogen, by removal of the protecting group to give compounds of Formula (D) wherein R_4 is hydrogen or, if "PG" was a protecting group other than a C_{1-6} alkyl group, the carboxylic acid (R_4 is hydrogen) can be converted to an ester wherein R_4 is C_{1-6} alkyl. Mono-*N*-substituted aminopyrazoles of Formula (C) or (D) can be converted to di-*N*-substituted aminopyrazoles of Formula (E) or (I) via a similar second reductive step and, if needed, a conversion of group "PG" to R_4 as described *supra*. The aldehyde or ketone used in this second reductive step can be the same or different to give symmetrical (i.e., R_1-A- = R_2-B-) or unsymmetrical (i.e., R_1-A- ≠ R_2-B-) di-*N*-subsituted aminopyrazoles respectively. Alternatively, amino-pyrazoles of Formula (B) can be converted to compounds of Formula (I) via a two part reductive amination utilizing only one procedural step; generally this method is useful for the preparation of symmetrical di-*N*-subsituted aminopyrazoles. In some embodiment, the Formulae described in Scheme I represent compounds wherein R_3 is hydrogen.

Another representative synthesis is set forth below in Scheme II for wherein R_3 is fluorine:

Scheme II



Compounds of the present invention, wherein R_3 is fluorine, can be prepared using several different approaches as shown in Scheme II. The fluorination step can be implemented at any point during the syntheses. For example, aminopyrazoles of Formula (F) can be fluorinated to give fluoropyrazoles of Formula (G), wherein R_3 is F. In accordance to the methods described in Scheme I, fluoropyrazoles of Formula (G) can be converted to compounds of Formulae (H, wherein R_3 is F), (J), (K) and (L). In one alternative manner, fluorine can be introduced in a later step. For example, mono-*N*-substituted aminopyrazoles of Formula (H), wherein R_3 is hydrogen, can undergo a fluorination step to give Compounds (J). Similarly, mono-*N*-substituted aminopyrazoles of Formula (H) can be converted to Compounds (K) and (L). Suitable fluorinating agents include, 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis-tetrafluoroborate (Selectfluor®), bis-(2-methoxyethyl)aminosulfur trifluoride (Deoxo-Fluor™), diethylaminosulfur trifluoride (DAST), bis(2-methoxyethyl)aminosulfur trifluoride (BAST), and the like.

One representative fluorinating procedure that can be used is as follows. A pyrazole, R_3 = H, (1 eq) is dissolved in a suitable solvent, such as acetonitrile, and selectfluor® (1 eq or more) is added. The resulting solution is heated to above RT, such as about 65°C, in a suitable reaction vessel, such as a sealed polypropylene flask, and the like, for a suitable time (monitored by an analytical method, such as, TLC, HPLC, and the like). The solvent is removed under reduced pressure, and the resulting crude product is taken up in a suitable solvent, such as dichloromethane, ethyl acetate and the like, and is washed with aqueous hydrochloric acid (for example, about 1M to 3M). The solvent is removed under reduced pressure and the residual purified, for example, by column chromatography (alumina, silica, and the like) to give the fluorinated pyrazole.

Preparation of compounds of the invention can involve the protection and deprotection of

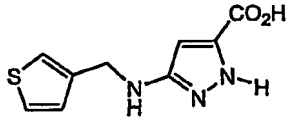
various chemical groups. The need for protection and deprotection, and the selection of appropriate protecting groups can be readily determined by one skilled in the art. The chemistry of protecting groups can be found, for example, in T.W. Green and P.G.M. Wuts, *Protective Groups in Organic Synthesis*, 3rd. Ed., Wiley & Sons, Inc., New York (1999), which is incorporated herein by reference in its entirety.

Reactions can be monitored according to any suitable method known in the art. For example, product formation can be monitored by spectroscopic means, such as nuclear magnetic resonance spectroscopy (e.g., ^{1}H or ^{13}C) infrared spectroscopy, spectrophotometry (e.g., UV-visible), or mass spectrometry, or by chromatography such as high performance liquid chromatography (HPLC) or thin layer chromatography.

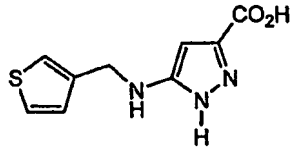
The various organic group transformations that can be utilized herein may be performed by a number of procedures other than those described above. References for other synthetic procedures that may be utililized for the preparation of intermediates or compounds disclosed herein may be found in, for example, Smith, M. B.; and March, J., *Advanced Organic Chemistry*, 5th Edition, Wiley-Interscience (2001); Larock, R.C., *Comprehensive Organic Transformations, A Guide to Functional Group Preparations*, 2nd Edition, VCH Publishers, Inc. (1999), or Wuts, P. G. M.; Greene, T. W.; *Protective Groups in Organic Synthesis*, 3rd Edition, John Wiley and Sons, (1999), all three are incorporated herein by reference their entirety.

Those of skill in the art will appreciate that a wide variety of compounds of the present invention can be prepared according to Schemes I and II.

It is understood that all tautomers of the compounds disclosed herein are within the scope of the invention. Further, based on the chemical formula there can be at least two different chemical names for the same compound, such chemical naming rules are known to those skilled in the art. For example, the compound shown below represents one possible tautomer and based on the chemical representation is appropriately named 5-[(thiophen-3-ylmethyl)-amino]-2H-pyrazole-3-carboxylic acid:



However, as discussed *supra*, this compound can also have another tautomeric form as shown below and based on this chemical representation is appropriately named 5-[(thiophen-3-ylmethyl)-amino]-1H-pyrazole-3-carboxylic acid:



Accordingly, there are at least two possible correct names for the same compound based on the chemical formula. It is understood that both of these names, as well as others based on the

priority of the attached groups, are correct and fully embraced by the present invention.

As will be recognized, the steps of the methods of the present invention need not be performed any particular number of times or in any particular sequence. Additional objects, advantages, and novel features of this invention will become apparent to those skilled in the art upon examination of the following examples thereof, which are intended to be illustrative and not intended to be limiting.

EXAMPLES

The following examples are presented for purposes of elucidation, and not limitation, of the present invention. One of ordinary skill in the art would be able to design equivalent assays and methods based on the disclosure herein, all of which form part of the present invention.

Example 1

Assays For determination of GPCR Activation

A variety of approaches are available for assessment of activation of human GPCRs. The following are illustrative; those of ordinary skill in the art are credited with the ability to determine those techniques that are preferentially beneficial for the needs of the artisan.

1. Membrane Binding Assays: [^{35}S]GTPγS Assay

When a G protein-coupled receptor is in its active state, either as a result of ligand binding or constitutive activation, the receptor couples to a G protein and stimulates the release of GDP and subsequent binding of GTP to the G protein. The alpha subunit of the G protein-receptor complex acts as a GTPase and slowly hydrolyzes the GTP to GDP, at which point the receptor normally is deactivated. Activated receptors continue to exchange GDP for GTP. The non-hydrolyzable GTP analog, [^{35}S]GTPγS, can be utilized to demonstrate enhanced binding of [^{35}S]GTPγS to membranes expressing activated receptors. The advantage of using [^{35}S]GTPγS binding to measure activation is that: (a) it is generically applicable to all G protein-coupled receptors; (b) it is proximal at the membrane surface making it less likely to pick-up molecules which affect the intracellular cascade.

The assay utilizes the ability of G protein coupled receptors to stimulate [^{35}S]GTPγS binding to membranes expressing the relevant receptors. The assay can, therefore, be used in the direct identification method to screen candidate compounds to endogenous GPCRs and non-endogenous, constitutively activated GPCRs. The assay is generic and has application to drug discovery at all G protein-coupled receptors.

The [^{35}S]GTPγS assay is incubated in 20 mM HEPES and between 1 and about 20mM $MgCl_2$ (this amount can be adjusted for optimization of results, although 20mM is preferred) pH 7.4, binding buffer with between about 0.3 and about 1.2 nM [^{35}S]GTPγS (this amount can be adjusted for optimization of results, although 1.2 is preferred) and 12.5 to 75 μg membrane

protein (*e.g*, 293 cells expressing the recombiriant GPCR; this amount can be adjusted for optimization) and 10 μM GDP (this amount can be changed for optimization) for 1 hour. Wheatgerm agglutinin beads (25 μl; Amersham) are then added and the mixture incubated for another 30 minutes at room temperature. The tubes are then centrifuged at 1500 x g for 5 minutes at room temperature and then counted in a scintillation counter.

2. Adenylyl Cyclase

A Flash Plate™ Adenylyl Cyclase kit (New England Nuclear; Cat. No. SMP004A) designed for cell-based assays can be modified for use with crude plasma membranes. The Flash Plate wells can contain a scintillant coating which also contains a specific antibody recognizing cAMP. The cAMP generated in the wells can be quantitated by a direct competition for binding of radioactive cAMP tracer to the cAMP antibody. The following serves as a brief protocol for the measurement of changes in cAMP levels in whole cells that express the receptors.

Transfected cells are harvested approximately twenty four hours after transient transfection. Media is carefully aspirated off and discarded. 10ml of PBS is gently added to each dish of cells followed by careful aspiration. 1ml of Sigma cell dissociation buffer and 3ml of PBS are added to each plate. Cells are pipetted off the plate and the cell suspension is collected into a 50ml conical centrifuge tube. Cells are then centrifuged at room temperature at 1,100 rpm for 5 min. The cell pellet is carefully re-suspended into an appropriate volume of PBS (about 3ml/plate). The cells are then counted using a hemocytometer and additional PBS is added to give the appropriate number of cells (with a final volume of about 50 μl/well).

cAMP standards and Detection Buffer (comprising 1 μCi of tracer [^{125}I] cAMP (50 μl) to 11 ml Detection Buffer) is prepared and maintained in accordance with the manufacturer's instructions. Assay Buffer is prepared fresh for screening and contains 50μl of Stimulation Buffer, 3ul of test compound (12μM final assay concentration) and 50μl cells. Assay Buffer is stored on ice until utilized. The assay, preferably carried out *e.g.* in a 96-well plate, is initiated by addition of 50μl of cAMP standards to appropriate wells followed by addition of 50ul of PBSA to wells H-11 and H12. 50μl of Stimulation Buffer is added to all wells. DMSO (or selected candidate compounds) is added to appropriate wells using a pin tool capable of dispensing 3μl of compound solution, with a final assay concentration of 12μM test compound and 100μl total assay volume. The cells are then added to the wells and incubated for 60 min at room temperature. 100μl of Detection Mix containing tracer cAMP is then added to the wells. Plates are then incubated additional 2 hours followed by counting in a Wallac MicroBeta scintillation counter. Values of cAMP/well are then extrapolated from a standard cAMP curve which is contained within each assay plate.

3. Cell-Based cAMP for Gi Coupled Target GPCRs

TSHR is a Gs coupled GPCR that causes the accumulation of cAMP upon activation. TSHR will be constitutively activated by mutating amino acid residue 623 (*i.e.*, changing an

alanine residue to an isoleucine residue). A Gi coupled receptor is expected to inhibit adenylyl cyclase, and, therefore, decrease the level of cAMP production, which can make assessment of cAMP levels challenging. An effective technique for measuring the decrease in production of cAMP as an indication of activation of a Gi coupled receptor can be accomplished by co-transfecting, most preferably, non-endogenous, constitutively activated TSHR (TSHR-A623I) (or an endogenous, constitutively active Gs coupled receptor) as a "signal enhancer" with a Gi linked target GPCR to establish a baseline level of cAMP. An endogenous Gi coupled receptor, or an non-endogenous receptor thereof, is then co-transfected with the signal enhancer, and it is this material that can be used for screening. We will utilize such approach to effectively generate a signal when a cAMP assay is used. In some embodiments, this approach is preferably used in the direct identification of candidate compounds against Gi coupled receptors. It is noted that for a Gi coupled GPCR, when this approach is used, an inverse agonist of the target GPCR will increase the cAMP signal and an agonist will decrease the cAMP signal.

On day one, $2x10^4$ 293 cells/well will be plated out. On day two, two reaction tubes will be prepared (the proportions to follow for each tube are per plate): tube A will be prepared by mixing 2μg DNA of each receptor transfected into the mammalian cells, for a total of 4μg DNA (*e.g.*, pCMV vector; pCMV vector with mutated THSR (TSHR-A623I); TSHR-A623I and GPCR, etc.) in 1.2ml serum free DMEM (Irvine Scientific, Irvine, CA); tube B will be prepared by mixing 120μl lipofectamine (Gibco BRL) in 1.2ml serum free DMEM. Tubes A and B will then be admixed by inversions (several times), followed by incubation at room temperature for 30-45min. The admixture is referred to as the "transfection mixture". Plated 293 cells will be washed with 1XPBS, followed by addition of 10ml serum free DMEM. 2.4ml of the transfection mixture will then be added to the cells, followed by incubation for 4hrs at 37°C/5% CO_2. The transfection mixture will then be removed by aspiration, followed by the addition of 25ml of DMEM/10% Fetal Bovine Serum. Cells will then be incubated at 37°C/5% CO_2. After 24hr incubation, cells will then be harvested and utilized for analysis.

A Flash Plate™ Adenylyl Cyclase kit (New England Nuclear; Cat. No. SMP004A) is designed for cell-based assays, but can be modified for use with crude plasma membranes depending on the need of the skilled artisan. The Flash Plate wells will contain a scintillant coating which also contains a specific antibody recognizing cAMP. The cAMP generated in the wells can be quantitated by a direct competition for binding of radioactive cAMP tracer to the cAMP antibody. The following serves as a brief protocol for the measurement of changes in cAMP levels in whole cells that express the receptors.

Transfected cells will be harvested approximately twenty four hours after transient transfection. Media will be carefully aspirated off and discarded. 10ml of PBS will be gently added to each dish of cells followed by careful aspiration. 1ml of Sigma cell dissociation buffer and 3ml of PBS will be added to each plate. Cells will be pipetted off the plate and the cell

suspension will be collected into a 50ml conical centrifuge tube. Cells will then be centrifuged at room temperature at 1,100 rpm for 5 min. The cell pellet will be carefully re-suspended into an appropriate volume of PBS (about 3ml/plate). The cells will then be counted using a hemocytometer and additional PBS is added to give the appropriate number of cells (with a final volume of about 50µl/well).

cAMP standards and Detection Buffer (comprising 1 µCi of tracer [^{125}I] cAMP (50 µl) to 11 ml Detection Buffer) will be prepared and maintained in accordance with the manufacturer's instructions. Assay Buffer should be prepared fresh for screening and contained 50µl of Stimulation Buffer, 3µl of test compound (12µM final assay concentration) and 50µl cells, Assay Buffer can be stored on ice until utilized. The assay can be initiated by addition of 50µl of cAMP standards to appropriate wells followed by addition of 50µl of PBSA to wells H-11 and H12. Fifty µl of Stimulation Buffer will be added to all wells. Selected compounds (*e.g.*, TSH) will be added to appropriate wells using a pin tool capable of dispensing 3µl of compound solution, with a final assay concentration of 12µM test compound and 100µl total assay volume. The cells will then be added to the wells and incubated for 60 min at room temperature. 100µl of Detection Mix containing tracer cAMP will then be added to the wells. Plates were then incubated additional 2 hours followed by counting in a Wallac MicroBeta scintillation counter. Values of cAMP/well will then be extrapolated from a standard cAMP curve which is contained within each assay plate.

EXAMPLE 2

Tissue Distribution of the disclosed human GPCRs

A. RT-PCR

RT-PCR was applied to confirm the expression and to determine the tissue distribution of several novel human GPCRs. Oligonucleotides utilized were GPCR-specific and the human multiple tissue cDNA panels (MTC, Clontech) as templates. Taq DNA polymerase (Stratagene) were utilized for the amplification in a 40µl reaction according to the manufacturer's instructions. 20µl of the reaction will be loaded on a 1.5% agarose gel to analyze the RT-PCR products. Table E below lists **RUP38,** the cycle conditions and the primers utilized.

By way of illustration, RT-PCR results for **RUP38** are shown in in Figure 2. **RUP25** (a GPCR related to **RUP38,** GeneBank accession number AB065876.1) is included in Figure 2 to indicate that the amplification is specific to **RUP38.**

TABLE E

Receptor Identifier	Cycle Conditions Min ('), Sec (") Cycles 2-4 repeated 30 times	5' Primer (SEQ.ID.NO.)	3' Primer (SEQ.ID.NO.)	DNA Fragment	Tissue Expression
RUP38	96° for 2'	CTACTATGT GCGGCGTTC	CCCTTCTTGG AATGGTTATT	852bp	Includes Adipocyte

	96° for 30" 55°C for 1' 72° for 2' 72° for 10'	A (1)	T (2)		
RUP25	96° for 2' 96° for 30" 55°C for 1' 72° for 2' 72° for 10'	CTGATGGAC AACTATGTG AGGCGTTGG (SEQ.ID.NO.:3)	GCTGAAGCTG CTGCACAAAT TTGCACC (SEQ.ID.NO.:4)	297bp	Includes Adipocyte

B. Affymetrix GeneChip® Technology

Amino acid sequences were submitted to Affymetrix for the designing and manufacturing of microarray containing oligonucleotides to monitor the expression levels of G protein-coupled receptors (GPCRs) using their GeneChip® Technology. Also present on the microaccray were probes for characterized human brain tissues from Harvard Brain Band or obtained from commercially available sources. RNA samples were amplified, labeled, hybridized to the microarray, and data analyzed according to manufacturer's instructions.

The tissues in Figure 1 (from left to right) are: monocytes (CD14+), monocytes (adherent), neutrophils, A-431, adipocte (primary), spleen, Jurkat, AXC-002 epidermis carcinoma, cervix, adipose, AXC-0009 pancreas adenocarcinoma, trachea, lung, AXC-0070 stomach adenocarcinoma, esophagus, placenta, bone marrow, olfactory bulb, salivary gland, pons (upper), thymus, breast, lymph node, prostate epithelial, thyroid, pons (lower), bone, pericardium, frontal cortex (superior BM9), heart, RAJI cells, substantia nigra, kidney, aortic smooth muscle cells (primary), AXC-0074 lung carcinoma, adrenal gland, preadipocyte (cultured), bladder, small intestine, skin, cerebellum, adipocyte (cultured), globus pallidus, aortic smooth muscle cells (cultured), PC-3, pituitary gland (male), pituitary gland (female), AXC-0078 pancreas carcinoma, AXC-0036 liver carcinoma, cingulated gyrus, colon, skeletal muscle, thalamus, aortic endothelial cells, CD34+ progenitor cells, testis, neural progenitor, prostate, aorta, AXC-0040 bladder carcinoma, whole brain, B-cells (CD19+), amygdala, liver, HUVEC, anterior hippocampus, hypothalamus anterior, AXC-0043 lymph lymphoblast, U87, mesenchymal stem cell, spinal cord, AXC-0073 bone osteosarcoma, AXC-0038 leucocyte promyeloblast, AXC-0086 leuocyte lymphoma.

Adipose tissues were monitored for the level of gene expression of each of the GPCRs represented on the microarray. GPCRs were determined to be expressed if the expression index was greater than 100 (based upon and according to manufacturer's instructions). The data was analyzed and had indicated that classification of GPCRs with an expression index greater than 100 was reasonable because a number of known GPCRs had previously been reported to be expressed in neuronal tissues with an expression index greater than 100.

Using the GeneChip, we discovered **RUP38** to have high levels of expression in adipocytes indicating that, for example, that **RUP38** may play a role in lipolysis (*see*, Goodman & Gilman's, The Pharmacological Basis of Therapeutics, 9th Edition, page 235 (1996). *See* Figure 1. Figure 1 is a plot representing the expression level of **RUP38** in various tissues. Based upon this data, RUP38 is highly expressed by primary adipocytes.

Example 3

Protocol: Direct Identification of Inverse Agonists and Agonists

[^{35}S]GTPγS ASSAY

A. Membrane Preparation

In some embodiments membranes comprising the Target GPCR of interest and for use in the identification of candidate compounds as, *e.g.*,. inverse agonists, agonists, or antagonists, are preferably prepared as follows:

a. Materials

"Membrane Scrape Buffer" is comprised of 20mM HEPES and 10mM EDTA, pH 7.4; "Membrane Wash Buffer" is comprised of 20 mM HEPES and 0.1 mM EDTA, pH 7.4; "Binding Buffer" is comprised of 20mM HEPES, 100 mM NaCl, and 10 mM $MgCl_2$, pH 7.4.

b. Procedure

All materials will be kept on ice throughout the procedure. Firstly, the media will be aspirated from a confluent monolayer of cells, followed by rinse with 10ml cold PBS, followed by aspiration. Thereafter, 5ml of Membrane Scrape Buffer will be added to scrape cells; this will be followed by transfer of cellular extract into 50ml centrifuge tubes (centrifuged at 20,000 rpm for 17 minutes at 4°C). Thereafter, the supernatant will be aspirated and the pellet will be resuspended in 30ml Membrane Wash Buffer followed by centrifuge at 20,000 rpm for 17 minutes at 4°C. The supernatant will then be aspirated and the pellet resuspended in Binding Buffer. This will then be homogenized using a Brinkman Polytron™ homogenizer (15-20 second bursts until the all material is in suspension). This is referred to herein as "Membrane Protein".

Bradford Protein Assay

Following the homogenization, protein concentration of the membranes will be determined using the Bradford Protein Assay (protein can be diluted to about 1.5mg/ml, aliquoted and frozen (-80°C) for later use; when frozen, protocol for use will be as follows: on the day of the assay, frozen Membrane Protein is thawed at room temperature, followed by vortex and then homogenized with a Polytron at about 12 x 1,000 rpm for about 5-10 seconds; it is noted that for multiple preparations, the homogenizer should be thoroughly cleaned between homogenization of different preparations).

a. Materials

Binding Buffer (as per above); Bradford Dye Reagent; Bradford Protein Standard will be utilized, following manufacturer instructions (Biorad, cat. no. 500-0006).

b. Procedure

Duplicate tubes will be prepared, one including the membrane, and one as a control "blank". Each contained 800µl Binding Buffer. Thereafter, 10µl of Bradford Protein Standard (1mg/ml) will be added to each tube, and 10µl of membrane Protein will then be added to just one tube (not the blank). Thereafter, 200µl of Bradford Dye Reagent will be added to each tube, followed by vortex of each. After five (5) minutes, the tubes will be re-vortexed and the material therein will be transferred to cuvettes. The cuvettes will then be read using a CECIL 3041 spectrophotometer, at wavelength 595.

Identification Assay

a. Materials

GDP Buffer consisted of 37.5 ml Binding Buffer and 2mg GDP (Sigma, cat. no. G-7127), followed by a series of dilutions in Binding Buffer to obtain 0.2 µM GDP (final concentration of GDP in each well was 0.1 µM GDP); each well comprising a candidate compound, has a final volume of 200µl consisting of 100µl GDP Buffer (final concentration, 0.1µM GDP), 50µl Membrane Protein in Binding Buffer, and 50µl [^{35}S]GTPγS (0.6 nM) in Binding Buffer (2.5 µl [^{35}S]GTPγS per 10ml Binding Buffer).

b. Procedure

Candidate compounds will be preferably screened using a 96-well plate format (these can be frozen at -80°C). Membrane Protein (or membranes with expression vector excluding the Target GPCR, as control), will be homogenized briefly until in suspension. Protein concentration will then be determined using the Bradford Protein Assay set forth above. Membrane Protein (and control) will then be diluted to 0.25mg/ml in Binding Buffer (final assay concentration, 12.5µg/well). Thereafter, 100 µl GDP Buffer was added to each well of a Wallac Scintistrip™ (Wallac). A 5ul pin-tool will then be used to transfer 5 µl of a candidate compound into such well (*i.e.*, 5µl in total assay volume of 200 µl is a 1:40 ratio such that the final screening concentration of the candidate compound is 10µM). Again, to avoid contamination, after each transfer step the pin tool should be rinsed in three reservoirs comprising water (1X), ethanol (1X) and water (2X) – excess liquid should be shaken from the tool after each rinse and dried with paper and kimwipes. Thereafter, 50 µl of Membrane Protein will be added to each well (a control well comprising membranes without the Target GPCR was also utilized), and pre-incubated for 5-10 minutes at room temperature. Thereafter, 50µl of [^{35}S]GTPγS (0.6 nM) in Binding Buffer will be added to each well, followed by incubation on a shaker for 60 minutes at room temperature (again, in this example, plates were covered with foil). The assay will then be stopped by spinning of the plates at 4000 RPM for 15 minutes at 22°C. The plates will then be aspirated with an 8 channel

manifold and sealed with plate covers. The plates will then be read on a Wallac 1450 using setting "Prot. #37" (as per manufacturer's instructions).

Example 4

Melanophore Technology

Melanophores are skin cells found in lower vertebrates. They contain pigmented organelles termed melanosomes. Melanophores are able to redistribute these melanosomes along a microtubule network upon G-protein coupled receptor (GPCR) activation. The result of this pigment movement is an apparent lightening or darkening of the cells. In melanophores, the decreased levels of intracellular cAMP that result from activation of a Gi-coupled receptor cause melanosomes to migrate to the center of the cell, resulting in a dramatic lightening in color. If cAMP levels are then raised, following activation of a Gs-coupled receptor, the melanosomes are re-dispersed and the cells appear dark again. The increased levels of diacylglycerol that result from activation of Gq-coupled receptors can also induce this re-dispersion. In addition, the technology is also suited to the study of certain receptor tyrosine kinases. The response of the melanophores takes place within minutes of receptor activation and results in a simple, robust color change. The response can be easily detected using a conventional absorbance microplate reader or a modest video imaging system. Unlike other skin cells, the melanophores derive from the neural crest and appear to express a full complement of signaling proteins. In particular, the cells express an extremely wide range of G-proteins and so are able to functionally express almost all GPCRs.

Melanophores can be utilized to identify compounds, including natural ligands, against GPCRs. This method can be conducted by introducing test cells of a pigment cell line capable of dispersing or aggregating their pigment in response to a specific stimulus and expressing an exogenous clone coding for the GCPR. A stimulant, *e.g.*, melatonin, sets an initial state of pigment disposition wherein the pigment is aggregated within the test cells if activation of the GPCR induces pigment dispersion. However, stimulating the cell with a stimulant to set an initial state of pigment disposition wherein the pigment is dispersed if activation of the GPCR induces pigment aggregation. The test cells are then contacted with chemical compounds, and it is determined whether the pigment disposition in the cells changed from the initial state of pigment disposition. Dispersion of pigments cells due to the candidate compound, including but not limited to a ligand, coupling to the GPCR will appear dark on a petri dish, while aggregation of pigments cells will appear light.

Materials and methods will be followed according to the disclosure of U.S. Patent Number 5,462,856 and U.S. Patent Number 6,051,386. These patent disclosures are hereby incorporated by reference in their entirety.

Melanophores were transfected by electroporation with plasmids coding for the GPCRs,

for example **RUP38**. Pre-screening of the GPCRs in melanophores was performed in the absence of nicotinic acid following the protocol below to determine the G protein coupling. This pre-screen evidenced that **RUP38** (Figure 3) is strongly Gi-coupled.

The cells were plated in 96-well plates (one receptor per plate). 48 hours post-transfection, half of the cells on each plate were treated with 10nM melatonin. Melatonin activates an endogenous Gi-coupled receptor in the melanophores and causes them to aggregate their pigment. The remaining half of the cells were transferred to serum-free medium 0.7X L-15 (Gibco). After one hour, the cells in serum-free media remained in a pigment-dispersed state while the melatonin-treated cells were in a pigment-aggregated state. At this point, the cells were treated with a dose response of nicotinic acid (Sigma). If the plated GPCRs bound to nicotinic acid, the melanophores would be expected to undergo a color change in response to the compound. If the receptor were either a Gs or Gq coupled receptor, then the melatonin-aggregated melanophores would undergo pigment dispersion. In contrast, if the receptor was a Gi-coupled receptor, then the pigment-dispersed cells would be expected to undergo a dose-dependent pigment aggregation.

As set forth herein, it is shown that **RUP38**, is Gi-coupled. Additionally, **RUP38** may be used in methods described herein to identify antagonists, agonists, inverse agonists, partial agonists, allosteric enhancers, and negative allosteric modulators. Preferably, the modulator is an agonist.

Example 5

Screening Data for Nicotinic Acid and 1-Isopropyl-1H-Benzotriazole-5-Carboxylic Acid in cAMP Assays

Figure 4 presents screening data via adenylyl cyclase assay for **RUP38**. Note that nicotinic acid does not activate inhibition of forskolin stimulated cAMP **RUP38**-expressing CHO cells whereas 1-Isopropyl-1H-benzotriazole-5-carboxylic acid does.

Example 6

***In Vitro* Biological Activity - cAMP**

A modified Flash Plate™ Adenylyl Cyclase kit (New England Nuclear; Cat. No. SMP004A) was utilized for direct identification of candidate compounds as agonists to **RUP38** in accordance with the following protocol:

CHO cells stably transfected with **RUP38** were harvested from flasks *via* non-enzymatic means. The cells were washed in PBS and resuspended in the manufacturer's Assay Buffer. Live cells were counted using a hemacytometer and Trypan blue exclusion, and the cell concentration was adjusted to $2x10^6$ cells/mL. cAMP standards and Detection Buffer (comprising 2 µCi of tracer [^{125}I]-cAMP (100 µl) to 11 mL Detection Buffer) were prepared and maintained in

accordance with the manufacturer's instructions. Candidate compounds identified as per above (if frozen, thawed at room temperature) were added to their respective wells (preferably wells of a 96-well plate) at increasing concentrations (3µl/well; 12µM final assay concentration). To these wells, 100,000 cells in 50µl of Assay Buffer were added and the mixture was then incubated for 30 minutes at room temperature, with gentle shaking. Following the incubation, 100µl of Detection Buffer was added to each well, followed by incubation for 2-24 hours. Plates were counted in a Wallac MicroBeta™ plate reader using "Prot. #31" (as per manufacturer instructions).

Example 7

SUMMARY FOR RUP38

A summary for **RUP38** is shown in Table F:

TABLE F

Receptor Identifier	Expression by Adipocytes or Adipose	Gi-Coupled (Lowers the Level of Intracellular cAMP)	Shown to Inhibit Intracellular Lipolysis	Early Identified Agonists
RUP38	yes	yes	yes	1-Isopropyl-1*H*-benzotriazole-5-carboxylic acid; and 3-(5-Bromo-2-ethoxy-phenyl)-acrylic acid

Example 8

Transgenic Mouse/Rat

The present invention also provides methods and compositions for the generation of mice and rats that express **RUP38** recombinant human antilipolytic GPCR polyeptide of the invention.

Methods of making transgenic animals such as mice and rats are well known to those of ordinary skill in the art, and any such method can be used in the present invention. Briefly, transgenic mammals can be produced, e.g., by transfecting a pluripotential stem cell such as an ES cell with a polynucleotide encoding **RUP38** polypeptide of the invention. Successfully transformed ES cells can then be introduced into an early stage embryo that is then implanted into the uterus of a mammal of the same species. In certain cases, the transformed ("transgenic") cells will comprise part of the germ line of the resulting animal and adult animals comprising the transgenic cells in the germ line can then be mated to other animals, thereby eventually producing

a population of transgenic animals that have the transgene in each of their cells and that can stably transmit the transgene to each of their offspring. Other methods of introducing the polynucleotide can be used, for example introducing the polynucleotide encoding **RUP38** polypeptide of the invention into a fertilized egg or early stage embryo via microinjection. Alternatively, the transgene may be introduced into an animal by infection of zygotes with a retrovirus containing the transgene [Jaenisch, R, Proc Natl Acad Sci USA (1976) 73:1260-4]. Methods of making transgenic mammals are described, e.g., in Wall et al., J Cell Biochem (1992) 49:113-20; Hogan et al., in Manipulating the Mouse Embryo. A Laboratory Manual. (1986) Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y.; in WO 91/08216; or in U.S. Patent No. 4,736, 866; all of which disclosures are hereby incorporated by reference in their entirety.

Example 9

Receptor Binding Assay

In addition to the methods described herein, another means for evaluating a test compound is by determining binding affinities to the **RUP38** receptor. This type of assay generally requires a radiolabelled ligand to the **RUP38** receptor. Absent the use of known ligands for the **RUP38** receptor and radiolabels thereof, compounds of Formula (I) can be labelled with a radioisotope and used in an assay for evaluating the affinity of a test compound to the **RUP38** receptor.

A radiolabelled **RUP38** compound of Formula (I) can be used in a screening assay to identify/evaluate compounds. In general terms, a newly synthesized or identified compound (i.e., test compound) can be evaluated for its ability to reduce binding of the "radiolabelled compound of Formula (I)" to the **RUP38** receptor. Accordingly, the ability to compete with the "radio-labelled compound of Formula (I)" or **Radiolabelled RUP38 Ligand** for the binding to the **RUP38** receptor directly correlates to its binding affinity of the test compound to the **RUP38** receptor.

ASSAY PROTOCOL FOR DETERMINING RECEPTOR BINDING FOR RUP38:

A. RUP38 RECEPTOR PREPARATION

293 cells (human kidney, ATCC), transiently transfected with 10 ug human **RUP38** receptor and 60 ul Lipofectamine (per 15-cm dish), are grown in the dish for 24 hours (75% confluency) with a media change and removed with 10 mL/dish of Hepes-EDTA buffer (20mM Hepes + 10 mM EDTA, pH 7.4). The cells are then centrifuged in a Beckman Coulter centrifuge for 20 minutes, 17,000 rpm (JA-25.50 rotor). Subsequently, the pellet is resuspended in 20 mM Hepes + 1 mM EDTA, pH 7.4 and homogenized with a 50- mL Dounce homogenizer and again centrifuged. After removing the supernatant, the pellets are stored at -80°C, until used in binding assay. When used in the assay, membranes are thawed on ice for 20 minutes and then 10 mL of

incubation buffer (20 mM Hepes, 1 mM $MgCl_2$,100 mM NaCl, pH 7.4) added. The membranes are then vortexed to resuspend the crude membrane pellet and homogenized with a Brinkmann PT-3100 Polytron homogenizer for 15 seconds at setting 6. The concentration of membrane protein is determined using the BRL Bradford protein assay.

B. BINDING ASSAY

For total binding, a total volume of 50ul of appropriately diluted membranes (diluted in assay buffer containing 50mM Tris HCl (pH 7.4), 10mM $MgCl_2$, and 1mM EDTA; 5-50ug protein) is added to 96-well polyproylene microtiter plates followed by addition of 100ul of assay buffer and 50ul of **Radiolabelled RUP38 Ligand**. For nonspecific binding, 50 ul of assay buffer is added instead of 100ul and an additional 50ul of 10uM cold **RUP38** is added before 50ul of **Radiolabelled RUP38 Ligand** is added. Plates are then incubated at room temperature for 60-120 minutes. The binding reaction is terminated by filtering assay plates through a Microplate Devices GF/C Unifilter filtration plate with a Brandell 96-well plate harvestor followed by washing with cold 50 mM Tris HCl, pH 7.4 containing 0.9% NaCl. Then, the bottom of the filtration plate are sealed, 50ul of Optiphase Supermix is added to each well, the top of the plates are sealed, and plates are counted in a Trilux MicroBeta scintillation counter. For compound competition studies, instead of adding 100ul of assay buffer, 100ul of appropriately diluted test compound is added to appropriate wells followed by addition of 50ul of **Radiolabelled RUP38 Ligand.**

C. CALCULATIONS

The test compounds are initially assayed at 1 and 0.1 μM and then at a range of concentrations chosen such that the middle dose would cause about 50% inhibition of a **Radio-RUP38 Ligand** binding (i.e., IC_{50}). Specific binding in the absence of test compound (B_O) is the difference of total binding (B_T) minus non-specific binding (NSB) and similarly specific binding (in the presence of test compound) (B) is the difference of displacement binding (B_D) minus non-specific binding (NSB). IC_{50} is determined from an inhibition response curve, logit-log plot of % B/B_O vs concentration of test compound.

K_i is calculated by the Cheng and Prustoff transformation:

$$K_i = IC_{50} / (1 + [L]/K_D)$$

where [L] is the concentration of a **Radio-RUP38 Ligand** used in the assay and K_D is the dissociation constant of a **Radio-RUP38 Ligand** determined independently under the same binding conditions.

Example 10

Chemistry - Syntheses of compounds of the present invention.

The compounds of the invention and their synthesis are further illustrated by the following examples. The following examples are provided to further define the invention without, however, limiting the invention to the particulas of these examples. The compounds described herein, *supra* and *infra* are named by CS Chem Draw Ultra Version 7.0.1.

Chemistry: Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded on a Varian Mercury Vx-400 equipped with a 4 nucleus auto switchable probe and z-gradient or a Bruker Avance-400 equipped with a QNP (Quad Nucleus Probe) or a BBI (Broad Band Inverse) and z-gradient. Chemical shifts are given in parts per million (ppm) with the residual solvent signal used as reference. NMR abbreviations are used as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. Microwave irradiations were carried out using the Smith Synthesizer (Personal Chemistry). Thin-layer chromatography (TLC) was performed on silica gel 60 F_{254} (Merck), preparatory thin-layer chromatography (prep TLC) was preformed on PK6F silica gel 60 A 1 mm plates (Whatman), and column chromatography was carried out on a silica gel column using Kieselgel 60, 0.063-0.200 mm (Merck). Evaporation was done in vacuo on a Buchi rotary evaporator. Celite 545 ® was used during palladium filtrations.
LCMS specs: 1) PC: HPLC-pumps: LC-10AD *VP*, Shimadzu Inc.; HPLC system controller: SCL-10A *VP*, Shimadzu Inc; UV-Detector: SPD-10A *VP*, Shimadzu Inc; Autosampler: CTC HTS, PAL, Leap Scientific; Mass spectrometer: API 150EX with Turbo Ion Spray source, AB/MDS Sciex; Software: Analyst 1.2. 2) Mac: HPLC-pumps: LC-8A *VP*, Shimadzu Inc; HPLC system controller: SCL-10A *VP*, Shimadzu Inc.
UV-Detector: SPD-10A *VP*, Shimadzu Inc; Autosampler: 215 Liquid Handler, Gilson Inc; Mass spectrometer: API 150EX with Turbo Ion Spray source, AB/MDS Sciex
Software: Masschrom 1.5.2.

Compound 1

Preparation of 5-Benzylamino-1H-pyrazole-3-carboxylic acid.

A solution of 5-Amino-1H-pyrazole-3-carboxylic acid ethyl ester (0.0775 g, 0.500 mmol), benzaldehyde (0.064 g, 0.60 mmol) and sodium triacetoxyborohydride (0.212 g, 1.00 mmol) in dichloroethane (5 cm^3) and stirred over night at 60°C. The solution was diluted with further dichloroethane (10 cm^3), was washed with $NaHCO_3$, until there was no further gas evolution, then with brine. The organic phase was dried over anhydrous Na_2SO_4, filtered, and solvent removed under reduced pressure to give a brown oil. The crude product was taken into acetonitrile (3 cm^3) and purified by preparatory HPLC to give 5-benzylamino-1H-pyrazole-3-carboxylic acid ethyl ester.

5-Benzylamino-1H-pyrazole-3-carboxylic acid ethyl ester was taken up in 1M lithium hydroxide: tetrahydrofuran : methanol (1 : 5 : 1) (10 cm^3)and heated at reflux over night. Solvent

was removed under reduced pressure and the crude product was acidified to pH 1 with 0.1M HCl and extracted with ethyl acetate (10 cm^3). The organic phase was dried over anhydrous Na_2SO_4, filtered, and solvent removed under reduced pressure to give a brown, glassy solid. ^1H (DMSO-d6): 7.35-7.2 (m, 5H, $CH_2C_6H_5$), 6.0 (s, 1H), 4.5 (s, 2H, $CH_2C_6H_5$). m/z (ES+): 218 [M+H]+

The intermediate 5-Amino-1H-pyrazole-3-carboxylic acid ethyl ester was prepared in the following manner:

A. 5-Nitro-1H-pyrazole-3-carboxylic acid ethyl ester.

To a solution of 5-Nitro-1H-pyrazole-3-carboxylic acid (5.000 g, 31.84 mmol) in absolute ethanol (50 cm^3) at room temperature under argon was added acetyl chloride (5.05mL, 5.55g, 70.1 mmol) dropwise over 2 minutes. The resulting solution was heated to reflux overnight. Solvent was removed under reduced pressure and the resulting solid dissolved in ethyl acetate (100 cm^3) and washed with aqueous saturated $NaHCO_3$ until neutral, brine, dried (anhydrous Na_2SO_4), filtered, and solvent removed under reduced pressure to give a yellow solid (5.20g, 88%). $^1H(CD_3OD)$: 7.4 (s, 1H), 4.4 (q, 2H, J=7.1, $CO_2CH_2CH_3$), 1.4 (t, 3H, J=7.1,$CO_2CH_2CH_3$). m/z (ES+): 186 [M+H]+

B. 5-Amino-1H-pyrazole-3-carboxylic acid ethyl ester.

To a solution of 5-Nitro-1H-pyrazole-3-carboxylic acid ethyl ester (0.925 g, 0.500 mmol) in absolute ethanol (10 cm^3) was added 10% Pd/C (0.100 g). The mixture was stirred under an atmosphere of H_2 at room temperature for 18 hours, filtered through Celite and the solvent removed under reduced pressure to give a green solid (0.70 g, 90%). ^1H (CD_3OD): 6.0 (s, 1H), 4.3 (q, 2H, J=7.1, $CO_2CH_2CH_3$), 1.4 (t, 3H, J=7.1,$CO_2CH_2CH_3$). m/z (ES+): 156 [M+H]+

Compound 2

Preparation of 5-sec-Butylamino-1H-pyrazole-3-carboxylic acid.

Compound **2** was prepared in a similar manner as described for Compound **1**, *supra*. $^1H(CD_3OD)$: 3.7-3.5 (m, 1H, $NHCH(CH_3)(C_2H_5)$), 1.8-1.7 (m, 1H, $NHCH(CH_3)(CHHCH_3)$), 1.65-1.54 (m, 1H, $NHCH(CH_3)(CHHCH_3)$) 1.30 (d, 3H, J=6.6, $NHCH(CH_3)(C_2H_5)$), 1.02 (t, 3H, J=7.5, $NHCH(CH_3)(CH_2CH_3)$). m/z (ES+): 184 [M+H]+

Compound 3

Preparation of 5-(1-Methyl-butylamino)-1H-pyrazole-3-carboxylic acid.

Compound 3 was prepared in a similar manner as described for Compound **1**, *supra*. ^1H (CD_3OD): 3.7-3.6 (m, 1H, $NHCH(CH_3)(C_3H_7)$), 1.7-1.6 (m, 1H, $NHCH(CH_3)(CHHC_2H_5)$), 1.6-1.4 (m, 3H, .$NHCH(CH_3)(CHHC_2H_3)$ & $NHCH(CH_3)(CH_2CH_2CH_3)$) 1.30 (d, 3H, J=6.5, $NHCH(CH_3)(C_3H_7)$), 0.97 (t, 3H, J=7.3, $NHCH(CH_3)((CH_2)_2CH_3)$). m/z (ES+): 198 [M+H]+

Compound 4

Preparation of 5-[(Thiophen-3-ylmethyl)-amino]-1H-pyrazole-3-carboxylic acid.

Compound 4 was prepared in a similar manner as described for Compound 1, *supra*. ^1H (CD_3OD): 7.38 (dd, 1H, J1=5.0, J2=3.0, C(5')-H), 7.31 (d, 1H, J=3.0, C(2')-H), 7.10 (d, 2H, J=5.0, C(4')-H), 5.96 (s, 1H, pyrazole-H), 4.38 (s, 2H, $NHCH_2$).
m/z (ES+): 224 [M+H]+, 206 [M-OH]+, 224 [M+H]+

Compound 5

Preparation of 5-[(5-Bromo-thiophen-2-ylmethyl)-amino]-1H-pyrazole-3-carboxylic acid.

Compound 5 was prepared in a similar manner as described for Compound 1, *supra*. m/z (ES+): 301 [M+H, 79Br]+, 303 [M+H, 81Br]+

Compound 6

Preparation of 5-Dibenzylamino-1H-pyrazole-3-carboxylic acid.

A solution of 5-Amino-1H-pyrazole-3-carboxylic acid ethyl ester (0.0775 g, 0.500 mmol), benzaldehyde (0.117 g, 1.10 mmol) and sodium triacetoxyborohydride (0.318 g, 1.50 mmol) in dichloroethane (2 cm^3) was allowed to react at 170°C for 1200 seconds utilizing Smith Synthesizer. The solution was diluted with further dichloroethane (10 cm^3), washed with $NaHCO_3$ until there was no further gas evolution, then with brine. The organic phase was dried over anhydrous Na_2SO_4, filtered, and solvent removed under reduced pressure to give a brown oil. The crude product was taken into acetonitrile (3 cm^3) and purified by preparatory HPLC to give 5-dibenzylamino-1H-pyrazole-3-carboxylic acid ethyl ester.

5-Dibenzylamino-1H-pyrazole-3-carboxylic acid ethyl ester was taken up in 1M lithium hydroxide: tetrahydrofuran : methanol (1 : 5 : 1) (10 cm^3) and heated at 65°C for 18 hours. Solvent was removed under reduced pressure and the crude product was taken to a pH of 1 with 0.1M aqueous HCl and extracted with ethyl acetate (10 cm^3). The organic phase was dried over anhydrous Na_2SO_4, filtered, and solvent removed under reduced pressure to give 5-(dibenzylamino)-1H-pyrazole-3-carboxylic acid as a brown, glassy solid. ^1H (DMSO-d_6): 7.35-7.2 (m, 10H, $(CH_2C_6H_5)_2$), 6.00 (s, 1H, pyrazole-H), 4.5 (s, 4H, $(CH_2C_6H_5)_2$). m/z (ES+): 308 [M+H]+

Compound 7

Preparation of 5-Dipropylamino-1H-pyrazole-3-carboxylic acid.

Compound 7 was prepared in a similar manner as described for Compound 6, *supra*. m/z (ES+): 212 [M+H]+.

Compound 8

Preparation of 5-(Bis-thiophen-3-ylmethyl-amino)-1H-pyrazole-3-carboxylic acid.

Compound **8** was prepared in a similar manner as described for Compound **6**, *supra*. ^{1}H (DMSO-d6): 7.35 (dd, 2H, J_1=4.9, J_2=3.0, C(5')-H), 7.17 (d, 2H, J=1.9, C(2')-H), 6.87 (d, 2H, J=4.9, C(4')-H), 5.96 (s, 1H, pyrazole-H), 4.27 (s, 4H, $N(CH_2Ar)_2$). m/z (ES+): 320 [M+H]+

Compound 9

Preparation of 5-(Bis-cyclopropylmethyl-amino)-1H-pyrrole-3-carboxylic acid.

Compound **9** was prepared in a similar manner as described for Compound **6**, *supra*. ^{1}H (DMSO-d6): 6.13 (s, 1H, pyrazole-H), 3.18 (d, 4H, $NH(CH_2cPr)_2$), 1.0-0.95 (m, 2H, CH[-CH_2CH_2-]), 0.45-0.39 (m, 4H), 0.22-0.18 (m, 4H). m/z (ES+): 236 [M+H]+, 218 [M-OH]+

Compound 10

Preparation of 5-[Bis-(3-methyl-butyl)-amino]-1H-pyrrole-3-carboxylic acid.

Compound **10** was prepared in a similar manner as described for Compound **6**, *supra*. ^{1}H (DMSO-d6): 5.97 (s, 1H, pyrazole-H), 3.17 (t, 4H, J=7.7, $NHCH_2$), 1.55 (septet, 2H, J=6.6, $CH(CH_3)_2$), 1.35 (q like, .4H, J=7.3, NCH_2CH_2), 0.89 (d, 12H, J=6.6, CH_3). m/z (ES+): 268 [M+H]+, 250 [M-OH]+

Compound 11

Preparation of 5-[Bis-(3-methyl-but-2-enyl)-amino]-1H-pyrrole-3-carboxylic acid.

Compound **11** was prepared in a similar manner as described for Compound **6**, *supra*. ^{1}H (DMSO-d6): 6.03 (s, 1H, pyrazole-H), 5.14 (t, 2H. J=6.6, -CH=), 3.73 (d, 4H, J=6.6, CH_2CH=), 1.67 (s, 6H, $=C(CH_3)_2$), 1.61 (s, 6H, $=C(CH_3)_2$). m/z (ES+): 264 [M+H]+

Compound 12

Preparation of 5-(Bis-cyclohexylmethyl-amino)-1H-pyrazole-3-carboxylic acid.

Compound **12** was prepared in a similar manner as described for Compound **6**, *supra*. ^{1}H (DMSO-d6): 5.89 (s, 1H, pyrazole-H), 3.03 (d, 4H, J=6.9, $NHCH_2$), 1.7-1.5 (m, 12H), 1.2-1.0 (m, 6H), 1.0-0.8 (m, 4H). m/z (ES+): 320 [M+H]+ 302 [M-OH]+

Compound 13

Preparation of 5-Diphenethylamino-1H-pyrazole-3-carboxylic acid.

Compound **3** was prepared in a similar manner as described for Compound **6**, *supra*. ^{1}H (DMSO-d6): 7.3-7.1 (m, 10H), .6.05 (s, 1H, pyr-H), 3.38 (t, 4H, J=7.7, NCH_2), 2.75 (t, 4H, J=7.7, NCH_2CH_2). m/z (ES+): 336 [M+H]+ 318 [M-OH]+

Compound 14

Preparation of 5-Dihexylamino-1H-pyrazole-3-carboxylic acid.

Compound **14** was prepared in a similar manner as described for Compound **6**, *supra*. ^{1}H (DMSO-d6): 5.98 (s, 1H, pyr-H), 3.15 (t, 4H, J=7.4, NCH_2), 1.5-1.4 (m, 4H), 1.3-1.2 (m, 12H), 0.85. (t, 6H, J=6.6, CH3). m/z (ES+): 296 [M+H]+ 278 [M-OH]+

Compound 15

Preparation of 5-(Bis-benzo[1,3]dioxol-4-ylmethyl-amino)-1H-pyrazole-3-carboxylic acid.

Compound **15** was prepared in a similar manner as described for Compound **6**, *supra*. ^{1}H (DMSO-d6): 6.85-6.65 (m, 6H), 3.07 (s, 1H, pyr-H), 5.98 (s, 4H, OCH_2O), 4.43 (s, 4H, J=7.4, NCH_2). m/z (ES+): 396 [M+H]+ 378 [M-OH]+

Compound 16

Preparation of 5-(Bis-thiophen-2-ylmethyl-amino)-1H-pyrazole-3-carboxylic acid.

Compound **16** was prepared in a similar manner as described for Compound **6**, *supra*. ^{1}H (CD_3OD): 7.3-7.2 (m, 2H, C(5')-H), 7.0-6.9 (m, 4H), 6.22 (s, 1H, pyrazole-H), 4.56 (s, 4H, NCH_2). m/z (ES+): 344 [M+Na]+,320 [M+H]+

Compound 17

Preparation of 5-[Bis-(5-methyl-thiophen-2-ylmethyl)-amino]-1H-pyrazole-3-carboxylic acid.

Compound **17** was prepared in a similar manner as described for Compound **6**, *supra*. m/z (ES+): 348 [M+H]+

Compound 18

Preparation of 5-(Bis-furan-3-ylmethyl-amino)-1H-pyrazole-3-carboxylic acid.

Compound **18** was prepared in a similar manner as described for Compound **6**, *supra*. ^{1}H (DMSO-d6): 7.6-7.5 (m, 4H), 6.35 (s, 2H, C(4')-H), 6.14 (s, 1H, pyrazole-H), 4.16 (s, 4H, NCH_2). m/z (ES+): 288 [M+H]+,270 [M-OH]+

Compound 19

Preparation of 5-[Bis-(5-bromo-thiophen-2-ylmethyl)-amino]-1H-pyrazole-3-carboxylic acid.

Compound **19** was prepared in a similar manner as described for Compound **6**, *supra*. ^{1}H (CD_3OD): 6.93 (d, 2H, J=3.7, C(3')-H), 6.77 (d, 2H, J=3.7, C(4')-H), 6.24 (s, 1H, pyrazole-H), 4.52 (s, 4H, NCH_2). m/z (ES+): 480 [M+H, ^{81}Br2]+, 478 [M+H, ^{79}Br^{81}Br]+, 476 [M+H, ^{79}Br2]+, 316 [M-$CH_2C_4H_2BrS$, ^{81}Br]+, 314 [M-$CH_2C_4H_2BrS$, ^{79}Br]+.

Compound 20

Preparation of 5-[Bis-(4-fluoro-benzyl)-amino]-1H-pyrazole-3-carboxylic acid.

Compound 20 was prepared in a similar manner as described for Compound 6, *supra*. ^{1}H (CD_3OD): 7.23 (dd, 4H, J1=8.4, J2=5.5, C(3')-H), 7.00 (t like, 4H, J=8.7, C(2')-H), 6.10 (s, 1H, pyr-H), 4.43 (s, 4H, NCH_2). m/z (ES+): 344 [M+H]+, 326 [M-OH]+

Compound 21

Preparation of 5-[Bis-(3-fluoro-benzyl)-amino]-1H-pyrazole-3-carboxylic acid.

Compound 21 was prepared in a similar manner as described for Compound 6, *supra*. ^{1}H (CD_3OD): 7.30 (dd, 2H, J1=13.9, J2=7.8, C(5')-H), 7.06 (d, 2H, J=7.6, C(6')-H), 7.0-6.9 (m, 4H, C(3')-H & C(4')-H), 6.06 (s, 1H, pyr-H), 4.50 (s, 4H, NCH_2). m/z (ES+): 344 [M+H]+, 326 [M-OH]+

Compound 22

Preparation of 5-[Bis-(2-fluoro-benzyl)-amino]-1H-pyrazole-3-carboxylic acid.

Compound 22 was prepared in a similar manner as described for Compound 6, *supra*. ^{1}H (CD_3OD): 7.3-7.2 (m, 4H, C(4')-H & C(6')-H), 7.1-7.0 (m, 4H, C(3')-H & C(5')-H), 6.09 (s, 1H, pyr-H), 4.57 (s, 4H, NCH_2). m/z (ES+): 344 [M+H]+, 326 [M-OH]+

Compound 23

Preparation of 5-(Benzyl-thiophen-3-ylmethyl-amino)-1H-pyrazole-3-carboxylic acid.

A solution of 5-(3'thiophenyl)amino-1H-pyrazole-3-carboxylic acid ethyl ester (0.100 g, 0.40 mmol), benzaldehyde (0.106 g, 1.00 mmol) and sodium triacetoxyborohydride (0.318 g, 1.50 mmol) in dichloroethane (10 cm^3) was stirred at 65°C for 18 hours. The solution was diluted with further dichloroethane (10 cm^3), washed with NaHCO3, until there was no further gas evolution, then with brine. The organic phase was dried over anhydrous Na_2SO_4, filtered, and solvent removed under reduced pressure. The crude product was taken into acetonitrile (3 cm^3) and purified by preparatory HPLC to give 5-(benzyl-thiophen-3-ylmethyl-amino)-1H-pyrazole-3-carboxylic acid ethyl ester.

5-(3'-thiophenyl)benzylamino-1H-pyrazole-3-carboxylic acid ethyl ester was taken up in 1M lithium hydroxide : tetrahydrofuran : methanol (1 : 5 : 1) (10 cm^3) and heated at 65oC for 18 hours. Solvent was removed under reduced pressure and the crude product was taken to a pH of 1 with 0.1M aqueous HCl and extracted with ethyl acetate (10 cm^3). The organic phase was dried over anhydrous Na_2SO_4, filtered, and solvent removed under reduced pressure to give 5-(benzyl-thiophen-3-ylmethyl-amino)-1H-pyrazole-3-carboxylic acid as a glassy brown solid (0.048g, 38%). ^{1}H (CD_3OD): 7.4-7.2 (m, 6H), 7.15-7.10 (m, 1H), 6.95 (dd, 1H, J1=5.0, J2=1.1), 6.08 (s, 1H, pyrazole-H), 4.43 (s, 2H, NCH_2), 4.40 (s, 2H, NCH_2). m/z (ES+): 314 [M+H]+, 296 [M-

OH]+

Compound 24

Preparation of 5-[(4-Fluoro-benzyl)-thiophen-3-ylmethyl-amino]-1H-pyrazole-3-carboxylic acid.

Compound 24 was prepared in a similar manner as described for Compound 23, *supra*. ^{1}H (CD_3OD): 7.3-7.2 (m, 3H, C(5')-H & C(2'')-H), 7.1-6.9 (m, 4H, C(2')-H, C(4')-H & C(3'')-H,), 6.06 (s, 1H, pyrazole-H), 4.42 (s, 4H, NCH_2). m/z (ES+): 332 [M+H]+

Compound 25

Preparation of 5-(Thiophen-2-ylmethyl-thiophen-3-ylmethyl-amino)-1H-pyrazole-3-carboxylic acid.

Compound 25 was prepared in a similar manner as described for Compound 23, *supra*. ^{1}H (CD_3OD): 7.35 (dd, 1H, J1=4.8, J2=3.0), 7.3-7.2 (m, 1H), 7.2-7.1 (m, 1H), 7.00 (d, 1H, J=5.0), 6.95-6.90 (m, 2H), 6.18 (s, 1H, pyr-H), 4.57 (s, 4H, NCH_2), 4.40 (s, 4H, NCH2). m/z (ES+): 320 [M+H]+

Compound 26

Preparation of 5-(Furan-2-ylmethyl-thiophen-3-ylmethyl-amino)-1H-pyrazole-3-carboxylic acid.

Compound 26 was prepared in a similar manner as described for Compound 23, *supra*. ^{1}H (CD_3OD): 7.32 (s, 1H), 7.24 (dd, 1H, J1=4.9, J2=3.0), 7.09 (s, 1H), 6.89 (d, 1H, J=5.0), 6.25-6.20 (m, 1H), 6.10-6.00 (m, 2H, inc pyr-H), 4.33 (s, 4H, NCH_2), 4.26 (s, 4H, NCH_2). m/z (ES+): 304 [M+H]+, 236 [M-C_4H_3O]+

Compound 27

Preparation of 5-(Furan-3-ylmethyl-thiophen-3-ylmethyl-amino)-1H-pyrazole-3-carboxylic acid.

Compound 27 was prepared in a similar manner as described for Compound 23, *supra*. ^{1}H (CD_3OD): 7.42-7.41 (m, 1H), 7.37-7.36 (m, 1H), 7.40-7.30 (m, 1H), 7.20-7.15 (m, 1H), 6.99 (d, 1H, J=5.0), 6.35-6.29 (m, 1H), 6.17 (s, 1H, pyr-H), 4.40 (s, 4H, NCH_2), 4.26 (s, 4H, NCH_2). m/z (ES+): 304 [M+H]+, 286 [M-OH]+

Example 16

***In Vitro* Biological Activities**

Certain compounds in the above examples were screened in the Membrane Cyclase Assay. Representative compounds are shown in the table below:

Compound	RUP38 (EC_{50}) Membrane Cyclase (μM)
6	1.84
23	0.21

The other compounds in the Examples showed EC_{50} activities in the membrane cyclase assay less than about 500 μM.

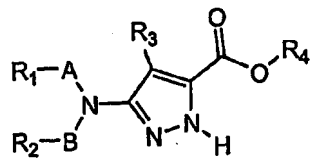
Throughout this application, various publications, patents and published patent applications are cited. The disclosures of these publications, patents and published patent applications referenced in this application are hereby incorporated by reference in their entirety into the present disclosure. Citation herein by Applicant of a publication, patent, or published patent application is not an admission by Applicant of said publication, patent, or published patent application as prior art. Modifications and extension of the disclosed inventions that are within the purview of the skilled artisan are encompassed within the above disclosure and the claims that follow.

A variety of expression vectors are available to those in the art for purposes of producing a polypeptide of interest in a cell. One suitable vector is pCMV, which is used in certain embodiments. This vector was deposited with the American Type Culture Collection (ATCC) on October 13, 1998 (10801 University Blvd., Manassas, VA 20110-2209 USA) under the provisions of the Budapest Treaty for the International Recognition of the Deposit of Microorganisms for the Purpose of Patent Procedure. The DNA was tested by the ATCC and determined to be viable. The ATCC has assigned the following deposit number to pCMV: ATCC #203351.

CLAIMS

What is claimed is:

1. A compound of Formula (I):



(I)

or a pharmaceutically acceptable salt, solvate or hydrate thereof;

wherein:

A is a C_{1-3} alkylene optionally substituted with 1, 2, 3, or 4 substituents selected independently from the group consisting of C_{1-6} alkoxy, C_{1-6} alkyl, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonyl, amino, C_{1-6} alkylamino, C_{2-6} dialkylamino, carbo-C_{1-6}-alkoxy, carboxy, cyano, C_{3-6} cycloalkyl, halogen, C_{1-6} haloalkoxy, C_{1-6} haloalkyl, C_{1-6} haloalkylsulfinyl, C_{1-6} haloalkylsulfonyl, C_{1-6} haloalkylthio and hydroxyl;

B is a C_{1-3} alkylene optionally substituted with 1, 2, 3, or 4 substituents selected independently from the group consisting of C_{1-6} alkoxy, C_{1-6} alkyl, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonyl, amino, C_{1-6} alkylamino, C_{2-6} dialkylamino, carbo-C_{1-6}-alkoxy, carboxy, cyano, C_{3-6} cycloalkyl, halogen, C_{1-6} haloalkoxy, C_{1-6} haloalkyl, C_{1-6} haloalkylsulfinyl, C_{1-6} haloalkylsulfonyl, C_{1-6} haloalkylthio and hydroxyl, or B is a bond;

R_1 is H, aryl, heteroaryl, C_{1-6} alkyl, C_{3-7} cycloalkyl, C_{2-6} alkenyl, or C_{1-6} haloalkyl, wherein said R_1 is optionally substituted with 1, 2, 3, 4, or 5 substituents selected independently from the group consisting of C_{1-6} acyl, acyloxy, C_{2-6} alkenyl, C_{1-6} alkoxy, C_{1-6} alkyl, C_{1-6} alkylcarboxamido, C_{2-6} alkynyl, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonyl, C_{1-6} alkylthio, C_{1-6} alkylureyl, amino, C_{1-6} alkylamino, C_{2-6} dialkylamino, carbo-C_{1-6}-alkoxy, carboxy, cyano, C_{3-6} cycloalkyl, C_{2-6} dialkylcarboxamido, halogen, C_{1-6} haloalkoxy, C_{1-6} haloalkyl, C_{1-6} haloalkylsulfinyl, C_{1-6} haloalkylsulfonyl, C_{1-6} haloalkylthio, hydroxyl, nitro and thiol, or two adjacent substituents together with the carbon atoms to which they are bonded form a C_{5-7} cycloalkyl or C_{5-7} heterocycloalkyl optionally substituted with 1, 2, 3, or 4 halogen atoms;

R_2 is H, aryl, heteroaryl, C_{1-6} alkyl, C_{3-7} cycloalkyl, C_{2-6} alkenyl, or C_{1-6} haloalkyl, wherein said R_2 is optionally substituted with 1, 2, 3, 4, or 5 substituents selected independently from the group consisting of C_{1-6} acyl, acyloxy, C_{2-6} alkenyl, C_{1-6} alkoxy, C_{1-6} alkyl, C_{1-6} alkylcarboxamido, C_{2-6} alkynyl, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonyl, C_{1-6} alkylthio, C_{1-6} alkylureyl, amino, C_{1-6}

alkylamino, C_{2-6} dialkylamino, carbo-C_{1-6}-alkoxy, carboxy, cyano, C_{3-6} cycloalkyl, C_{2-6} dialkylcarboxamido, halogen, C_{1-6} haloalkoxy, C_{1-6} haloalkyl, C_{1-6} haloalkylsulfinyl, C_{1-6} haloalkylsulfonyl, C_{1-6} haloalkylthio, hydroxyl, nitro and thiol, or two adjacent substituents together with the carbon atoms to which they are bonded form a C_{5-7} cycloalkyl or C_{5-7} heterocycloalkyl optionally substituted with 1, 2, 3, or 4 halogen atoms;

R_3 is selected from the group consisting of H, C_{1-6} acyl, acyloxy, C_{2-6} alkenyl, C_{1-6} alkoxy, C_{1-6} alkyl, C_{1-6} alkylcarboxamido, C_{2-6} alkynyl, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonyl, C_{1-6} alkylthio, C_{1-6} alkylureyl, amino, C_{1-6} alkylamino, C_{3-6} dialkylamino, carbo-C_{1-6}-alkoxy, carboxy, cyano, C_{3-6} cycloalkyl, C_{2-6} dialkylcarboxamido, halogen, C_{1-6} haloalkoxy, C_{1-6} haloalkyl, C_{1-6} haloalkylsulfinyl, C_{1-6} haloalkylsulfonyl, C_{1-6} haloalkylthio, hydroxyl, nitro and thiol; and

R_4 is H or C_{1-6} alkyl.

2. The compound according to claim 1 wherein R_1 is H.

3. The compound according to claim 1 wherein R_1 is aryl optionally substituted with 1, 2, 3, 4, or 5 substituents selected independently from the group consisting of C_{1-6} acyl, acyloxy, C_{2-6} alkenyl, C_{1-6} alkoxy, C_{1-6} alkyl, C_{1-6} alkylcarboxamido, C_{2-6} alkynyl, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonyl, C_{1-6} alkylthio, C_{1-6} alkylureyl, amino, C_{1-6} alkylamino, C_{2-6} dialkylamino, carbo-C_{1-6}-alkoxy, carboxy, cyano, C_{3-6} cycloalkyl, C_{2-6} dialkylcarboxamido, halogen, C_{1-6} haloalkoxy, C_{1-6} haloalkyl, C_{1-6} haloalkylsulfinyl, C_{1-6} haloalkylsulfonyl, C_{1-6} haloalkylthio, hydroxyl, nitro and thiol.

4. The compound according to claim 1 wherein R_1 is aryl optionally substituted with 1, 2, 3, 4, or 5 substituents selected independently from the group consisting of C_{1-6} acyl, C_{2-6} alkenyl, C_{1-6} alkoxy, C_{1-6} alkyl, C_{1-6} alkylcarboxamido, C_{2-6} alkynyl, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonyl, C_{1-6} alkylthio, C_{1-6} alkylureyl, C_{1-6} alkylamino, C_{2-6} dialkylamino, carbo-C_{1-6}-alkoxy, carboxy, cyano, C_{3-6} cycloalkyl, C_{2-6} dialkylcarboxamido, halogen, C_{1-6} haloalkoxy, C_{1-6} haloalkyl, C_{1-6} haloalkylsulfinyl, C_{1-6} haloalkylsulfonyl, hydroxyl and nitro.

5. The compound according to claim 1 wherein R_1 is aryl optionally substituted with 1, 2, 3, 4 or 5 substituents selected independently from the group consisting of C_{1-6} acyl, C_{1-6} alkoxy, C_{1-6} alkyl, C_{1-6} alkylamino, C_{2-6} dialkylamino, carbo-C_{1-6}-alkoxy, carboxy, cyano, halogen, C_{1-6} haloalkoxy, C_{1-6} haloalkyl, hydroxyl and nitro.

6. The compound according to claim 1 wherein R_1 is aryl optionally substituted with 1, 2, 3, 4 or 5 substituents selected independently from the group consisting of C_{1-6} alkoxy, C_{1-6} alkyl, carboxy, cyano, halogen, C_{1-6} haloalkoxy, and C_{1-6} haloalkyl.

7. The compound according to claim 1 wherein R_1 is aryl optionally substituted with two adjacent substituents together with said aryl form a C_{5-7} cycloalkyl optionally substituted with halogen.

8. The compound according to claim 1 wherein R_1 is aryl optionally substituted with two adjacent substituents together with said aryl form a C_{5-7} heterocycloalkyl optionally substituted with halogen.

9. The compound according to claim 1 wherein R_1 is a benzo[1,3]dioxolyl.

10. The compound according to claim 1 wherein R_1 is heteroaryl optionally substituted with 1, 2, 3, or 4 substituents selected independently from the group consisting of C_{1-6} acyl, acyloxy, C_{2-6} alkenyl, C_{1-6} alkoxy, C_{1-6} alkyl, C_{1-6} alkylcarboxamido, C_{2-6} alkynyl, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonyl, C_{1-6} alkylthio, C_{1-6} alkylureyl, amino, C_{1-6} alkylamino, C_{2-6} dialkylamino, carbo-C_{1-6}-alkoxy, carboxy, cyano, C_{3-6} cycloalkyl, C_{2-6} dialkylcarboxamido, halogen, C_{1-6} haloalkoxy, C_{1-6} haloalkyl, C_{1-6} haloalkylsulfinyl, C_{1-6} haloalkylsulfonyl, C_{1-6} haloalkylthio, hydroxyl, nitro and thiol.

11. The compound according to claim 1 wherein R_1 is heteroaryl optionally substituted with 1, 2, 3, or 4 substituents selected independently from the group consisting of C_{1-6} acyl, C_{2-6} alkenyl, C_{1-6} alkoxy, C_{1-6} alkyl, C_{1-6} alkylcarboxamido, C_{2-6} alkynyl, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonyl, C_{1-6} alkylthio, C_{1-6} alkylureyl, C_{1-6} alkylamino, C_{2-6} dialkylamino, carbo-C_{1-6}-alkoxy, carboxy, cyano, C_{3-6} cycloalkyl, C_{2-6} dialkylcarboxamido, halogen, C_{1-6} haloalkoxy, C_{1-6} haloalkyl, C_{1-6} haloalkylsulfinyl, C_{1-6} haloalkylsulfonyl, hydroxyl, nitro and thiol.

12. The compound according to claim 1 wherein R_1 is heteroaryl optionally substituted with 1, 2, 3, or 4 substituents selected independently from the group consisting of C_{1-6} acyl, C_{1-6} alkoxy, C_{1-6} alkyl, C_{1-6} alkylamino, C_{2-6} dialkylamino, carbo-C_{1-6}-alkoxy, carboxy, cyano, halogen, C_{1-6} haloalkoxy, C_{1-6} haloalkyl, hydroxyl and nitro.

13. The compound according to claim 1 wherein R_1 is heteroaryl optionally substituted with

1, 2, 3, or 4 substituents selected independently from the group consisting of C_{1-6} alkoxy, C_{1-6} alkyl, carboxy, cyano, halogen, C_{1-6} haloalkoxy, C_{1-6} haloalkyl.

14. The compound according to any one of claims 10 to 13 wherein said heteroaryl is a 5-member or 6-member heteroaryl.

15. The compound according to claim 14 wherein said 5-member heteroaryl is selected from the group consisting of a furanyl, an isoxazolyl, an oxazolyl, an [1,2,4]-oxadiazolyl, an [1,3,4]-oxadiazolyl, a thienyl, an isothiazolyl, a thiazolyl, a [1,2,4]-thiadiazolyl, a [1,3,4-thiadiazolyl, a 1H-pyrrolyl, a 1H-pyrazolyl, an 1H-imidazolyl, a 1H-[1,2,4]-triazolyl, a 1H-[1,2,4]-triazolyl, and a 1H-tetrazolyl.

16. The compound according to claim 14 wherein said 5-member heteroaryl is selected from the group consisting of thiophen-2-yl, thiophen-3-yl, furan-2-yl and furan-3-yl.

17. The compound according to claim 14 wherein said 6-member heteroaryl is selected from the group consisting of a pyridyl, a pyrazine, and a pyrimidinyl.

18. The compound according to claim 14 wherein said pyridyl is pyridin-2-yl, pyridin-3-yl, or pyridin-4-yl.

19. The compound according to claim 1 wherein R_1 is C_{1-6} alkyl optionally substituted with 1, 2, 3, 4 or 5 substituents selected independently from the group consisting of C_{1-6} acyl, acyloxy, C_{2-6} alkenyl, C_{1-6} alkoxy, C_{1-6} alkyl, C_{1-6} alkylcarboxamido, C_{2-6} alkynyl, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonyl, C_{1-6} alkylthio, C_{1-6} alkylureyl, amino, C_{1-6} alkylamino, C_{2-6} dialkylamino, carbo-C_{1-6}-alkoxy, carboxy, cyano, C_{3-6} cycloalkyl, C_{2-6} dialkylcarboxamido, halogen, C_{1-6} haloalkoxy, C_{1-6} haloalkyl, C_{1-6} haloalkylsulfinyl, C_{1-6} haloalkylsulfonyl, C_{1-6} haloalkylthio, hydroxyl, nitro and thiol.

20. The compound according to claim 1 wherein R_1 is C_{1-6} alkyl optionally substituted with 1, 2, 3, 4 or 5 substituents selected independently from the group consisting of C_{1-6} acyl, C_{2-6} alkenyl, C_{1-6} alkoxy, C_{1-6} alkyl, C_{1-6} alkylcarboxamido, C_{2-6} alkynyl, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonyl, C_{1-6} alkylthio, C_{1-6} alkylureyl, C_{1-6} alkylamino, C_{2-6} dialkylamino, carbo-C_{1-6}-alkoxy, carboxy, cyano, C_{3-6} cycloalkyl, C_{2-6} dialkylcarboxamido, halogen, C_{1-6} haloalkoxy, C_{1-6} haloalkyl, C_{1-6} haloalkylsulfinyl, C_{1-6} haloalkylsulfonyl, hydroxyl and nitro.

21. The compound according to claim 1 wherein R_1 is C_{1-6} alkyl optionally substituted with 1, 2, 3, 4 or 5 substituents selected independently from the group consisting of C_{1-6} acyl, C_{1-6} alkoxy, C_{1-6} alkyl, C_{1-6} alkylamino, C_{2-6} dialkylamino, carbo-C_{1-6}-alkoxy, carboxy, cyano, halogen, C_{1-6} haloalkoxy, C_{1-6} haloalkyl, hydroxyl and nitro.

22. The compound according to claim 1 wherein R_1 is C_{1-6} alkyl optionally substituted with 1, 2, 3, 4 or 5 substituents selected independently from the group consisting of C_{1-6} alkoxy, C_{1-6} alkyl, carboxy, cyano, halogen, C_{1-6} haloalkoxy, and C_{1-6} haloalkyl.

23. The compound according to claim 1 wherein R_1 is C_{3-7} cycloalkyl optionally substituted with 1, 2, 3, 4 or 5 substituents selected independently from the group consisting of C_{1-6} alkoxy, C_{1-6} alkyl, carboxy, cyano, halogen, C_{1-6} haloalkoxy, and C_{1-6} haloalkyl.

24. The compound according to claim 1 wherein R_1 is C_{2-6} alkenyl optionally substituted with 1, 2, 3, 4 or 5 substituents selected independently from the group consisting of C_{1-6} acyl, acyloxy, C_{2-6} alkenyl, C_{1-6} alkoxy, C_{1-6} alkyl, C_{1-6} alkylcarboxamido, C_{2-6} alkynyl, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonyl, C_{1-6} alkylthio, C_{1-6} alkylureyl, amino, C_{1-6} alkylamino, C_{2-6} dialkylamino, carbo-C_{1-6}-alkoxy, carboxy, cyano, C_{3-6} cycloalkyl, C_{2-6} dialkylcarboxamido, halogen, C_{1-6} haloalkoxy, C_{1-6} haloalkyl, C_{1-6} haloalkylsulfinyl, C_{1-6} haloalkylsulfonyl, C_{1-6} haloalkylthio, hydroxyl, nitro and thiol.

25. The compound according to claim 1 wherein R_1 is C_{2-6} alkenyl optionally substituted with 1, 2, 3, 4 or 5 substituents selected independently from the group consisting of C_{1-6} alkoxy, C_{1-6} alkyl, carboxy, cyano, halogen, C_{1-6} haloalkoxy, and C_{1-6} haloalkyl.

26. The compound according to claim 1 wherein R_1 is C_{1-6} haloalkyl optionally substituted with 1, 2, 3, 4 or 5 substituents selected independently from the group consisting of C_{1-6} acyl, acyloxy, C_{2-6} alkenyl, C_{1-6} alkoxy, C_{1-6} alkyl, C_{1-6} alkylcarboxamido, C_{2-6} alkynyl, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonyl, C_{1-6} alkylthio, C_{1-6} alkylureyl, amino, C_{1-6} alkylamino, C_{2-6} dialkylamino, carbo-C_{1-6}-alkoxy, carboxy, cyano, C_{3-6} cycloalkyl, C_{2-6} dialkylcarboxamido, halogen, C_{1-6} haloalkoxy, C_{1-6} haloalkylsulfinyl, C_{1-6} haloalkylsulfonyl, C_{1-6} haloalkylthio, hydroxyl, nitro and thiol.

27. The compound according to claim 1 wherein R_1 is C_{1-6} haloalkyl optionally substituted with 1, 2, 3, 4 or 5 substituents selected independently from the group consisting of C_{1-6} alkoxy, C_{1-6} alkyl, carboxy, cyano, halogen, and C_{1-6} haloalkoxy.

28. The compound according to claim 1 wherein R_2 is H.

29. The compound according to claim 1 wherein R_2 is aryl optionally substituted with 1, 2, 3, 4, or 5 substituents selected independently from the group consisting of C_{1-6} acyl, acyloxy, C_{2-6} alkenyl, C_{1-6} alkoxy, C_{1-6} alkyl, C_{1-6} alkylcarboxamido, C_{2-6} alkynyl, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonyl, C_{1-6} alkylthio, C_{1-6} alkylureyl, amino, C_{1-6} alkylamino, C_{2-6} dialkylamino, carbo-C_{1-6}-alkoxy, carboxy, cyano, C_{3-6} cycloalkyl, C_{2-6} dialkylcarboxamido, halogen, C_{1-6} haloalkoxy, C_{1-6} haloalkyl, C_{1-6} haloalkylsulfinyl, C_{1-6} haloalkylsulfonyl, C_{1-6} haloalkylthio, hydroxyl, nitro and thiol.

30. The compound according to claim 1 wherein R_2 is aryl optionally substituted with 1, 2, 3, 4, or 5 substituents selected independently from the group consisting of C_{1-6} acyl, C_{2-6} alkenyl, C_{1-6} alkoxy, C_{1-6} alkyl, C_{1-6} alkylcarboxamido, C_{2-6} alkynyl, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonyl, C_{1-6} alkylthio, C_{1-6} alkylureyl, C_{1-6} alkylamino, C_{2-6} dialkylamino, carbo-C_{1-6}-alkoxy, carboxy, cyano, C_{3-6} cycloalkyl, C_{2-6} dialkylcarboxamido, halogen, C_{1-6} haloalkoxy, C_{1-6} haloalkyl, C_{1-6} haloalkylsulfinyl, C_{1-6} haloalkylsulfonyl, hydroxyl and nitro.

31. The compound according to claim 1 wherein R_2 is aryl optionally substituted with 1, 2, 3, 4 or 5 substituents selected independently from the group consisting of C_{1-6} acyl, C_{1-6} alkoxy, C_{1-6} alkyl, C_{1-6} alkylamino, C_{2-6} dialkylamino, carbo-C_{1-6}-alkoxy, carboxy, cyano, halogen, C_{1-6} haloalkoxy, C_{1-6} haloalkyl, hydroxyl and nitro.

32. The compound according to claim 1 wherein R_2 is aryl optionally substituted with 1, 2, 3, 4 or 5 substituents selected independently from the group consisting of C_{1-6} alkoxy, C_{1-6} alkyl, carboxy, cyano, halogen, C_{1-6} haloalkoxy, and C_{1-6} haloalkyl.

33. The compound according to claim 1 wherein R_2 is aryl optionally substituted with two adjacent substituents together with said aryl form a C_{5-7} cycloalkyl optionally substituted with halogen.

34. The compound according to claim 1 wherein R_2 is aryl optionally substituted with two adjacent substituents together with said aryl form a C_{5-7} heterocycloalkyl optionally substituted with halogen.

35. The compound according to claim 1 wherein R_2 is a benzo[1,3]dioxolyl.

36. The compound according to claim 1 wherein R_2 is heteroaryl optionally substituted with

1, 2, 3, or 4 substituents selected independently from the group consisting of C_{1-6} acyl, acyloxy, C_{2-6} alkenyl, C_{1-6} alkoxy, C_{1-6} alkyl, C_{1-6} alkylcarboxamido, C_{2-6} alkynyl, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonyl, C_{1-6} alkylthio, C_{1-6} alkylureyl, amino, C_{1-6} alkylamino, C_{2-6} dialkylamino, carbo-C_{1-6}-alkoxy, carboxy, cyano, C_{3-6} cycloalkyl, C_{2-6} dialkylcarboxamido, halogen, C_{1-6} haloalkoxy, C_{1-6} haloalkyl, C_{1-6} haloalkylsulfinyl, C_{1-6} haloalkylsulfonyl, C_{1-6} haloalkylthio, hydroxyl, nitro and thiol.

37. The compound according to claim 1 wherein R_2 is heteroaryl optionally substituted with 1, 2, 3, or 4 substituents selected independently from the group consisting of C_{1-6} acyl, C_{2-6} alkenyl, C_{1-6} alkoxy, C_{1-6} alkyl, C_{1-6} alkylcarboxamido, C_{2-6} alkynyl, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonyl, C_{1-6} alkylthio, C_{1-6} alkylureyl, C_{1-6} alkylamino, C_{2-6} dialkylamino, carbo-C_{1-6}-alkoxy, carboxy, cyano, C_{3-6} cycloalkyl, C_{2-6} dialkylcarboxamido, halogen, C_{1-6} haloalkoxy, C_{1-6} haloalkyl, C_{1-6} haloalkylsulfinyl, C_{1-6} haloalkylsulfonyl, hydroxyl, nitro and thiol.

38. The compound according to claim 1 wherein R_2 is heteroaryl optionally substituted with 1, 2, 3, or 4 substituents selected independently from the group consisting of C_{1-6} acyl, C_{1-6} alkoxy, C_{1-6} alkyl, C_{1-6} alkylamino, C_{2-6} dialkylamino, carbo-C_{1-6}-alkoxy, carboxy, cyano, halogen, C_{1-6} haloalkoxy, C_{1-6} haloalkyl, hydroxyl and nitro.

39. The compound according to claim 1 wherein R_2 is heteroaryl optionally substituted with 1, 2, 3, or 4 substituents selected independently from the group consisting of C_{1-6} alkoxy, C_{1-6} alkyl, carboxy, cyano, halogen, C_{1-6} haloalkoxy, C_{1-6} haloalkyl.

40. The compound according to any one of claims 36 to 39 wherein said heteroaryl is a 5-member or 6-member heteroaryl.

41. The compound according to claim 40 wherein said 5-member heteroaryl is selected from the group consisting of a furanyl, an isoxazolyl, an oxazolyl, an [1,2,4]-oxadiazolyl, an [1,3,4]-oxadiazolyl, a thienyl, an isothiazolyl, a thiazolyl, a [1,2,4]-thiadiazolyl, a [1,3,4-thiadiazolyl, a 1H-pyrrolyl, a 1H-pyrazolyl, an 1H-imidazolyl, a 1H-[1,2,4]-triazolyl, a 1H-[1,2,4]-triazolyl, and a 1H-tetrazolyl.

42. The compound according to claim 40 wherein said 5-member heteroaryl is selected from the group consisting of thiophen-2-yl, thiophen-3-yl, furan-2-yl and furan-3-yl.

43. The compound according to claim 40 wherein said 6-member heteroaryl is selected from

the group consisting of a pyridyl, a pyrazine, and a pyrimidinyl.

44. The compound according to claim 40 wherein said pyridyl is pyridin-2-yl, pyridin-3-yl, or pyridin-4-yl.

45. The compound according to claim 1 wherein R_2 is C_{1-6} alkyl optionally substituted with 1, 2, 3, 4 or 5 substituents selected independently from the group consisting of C_{1-6} acyl, acyloxy, C_{2-6} alkenyl, C_{1-6} alkoxy, C_{1-6} alkyl, C_{1-6} alkylcarboxamido, C_{2-6} alkynyl, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonyl, C_{1-6} alkylthio, C_{1-6} alkylureyl, amino, C_{1-6} alkylamino, C_{2-6} dialkylamino, carbo-C_{1-6}-alkoxy, carboxy, cyano, C_{3-6} cycloalkyl, C_{2-6} dialkylcarboxamido, halogen, C_{1-6} haloalkoxy, C_{1-6} haloalkyl, C_{1-6} haloalkylsulfinyl, C_{1-6} haloalkylsulfonyl, C_{1-6} haloalkylthio, hydroxyl, nitro and thiol.

46. The compound according to claim 1 wherein R_2 is C_{1-6} alkyl optionally substituted with 1, 2, 3, 4 or 5 substituents selected independently from the group consisting of C_{1-6} acyl, C_{2-6} alkenyl, C_{1-6} alkoxy, C_{1-6} alkyl, C_{1-6} alkylcarboxamido, C_{2-6} alkynyl, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonyl, C_{1-6} alkylthio, C_{1-6} alkylureyl, C_{1-6} alkylamino, C_{2-6} dialkylamino, carbo-C_{1-6}-alkoxy, carboxy, cyano, C_{3-6} cycloalkyl, C_{2-6} dialkylcarboxamido, halogen, C_{1-6} haloalkoxy, C_{1-6} haloalkyl, C_{1-6} haloalkylsulfinyl, C_{1-6} haloalkylsulfonyl, hydroxyl and nitro.

47. The compound according to claim 1 wherein R_2 is C_{1-6} alkyl optionally substituted with 1, 2, 3, 4 or 5 substituents selected independently from the group consisting of C_{1-6} acyl, C_{1-6} alkoxy, C_{1-6} alkyl, C_{1-6} alkylamino, C_{2-6} dialkylamino, carbo-C_{1-6}-alkoxy, carboxy, cyano, halogen, C_{1-6} haloalkoxy, C_{1-6} haloalkyl, hydroxyl and nitro.

48. The compound according to claim 1 wherein R_2 is C_{1-6} alkyl optionally substituted with 1, 2, 3, 4 or 5 substituents selected independently from the group consisting of C_{1-6} alkoxy, C_{1-6} alkyl, carboxy, cyano, halogen, C_{1-6} haloalkoxy, and C_{1-6} haloalkyl.

49. The compound according to claim 1 wherein R_2 is C_{3-7} cycloalkyl optionally substituted with 1, 2, 3, 4 or 5 substituents selected independently from the group consisting of C_{1-6} alkoxy, C_{1-6} alkyl, carboxy, cyano, halogen, C_{1-6} haloalkoxy, and C_{1-6} haloalkyl.

50. The compound according to claim 1 wherein R_2 is C_{2-6} alkenyl optionally substituted with 1, 2, 3, 4 or 5 substituents selected independently from the group consisting of C_{1-6} acyl, acyloxy, C_{2-6} alkenyl, C_{1-6} alkoxy, C_{1-6} alkyl, C_{1-6} alkylcarboxamido, C_{2-6} alkynyl, C_{1-6}

alkylsulfinyl, C_{1-6} alkylsulfonyl, C_{1-6} alkylthio, C_{1-6} alkylureyl, amino, C_{1-6} alkylamino, C_{2-6} dialkylamino, carbo-C_{1-6}-alkoxy, carboxy, cyano, C_{3-6} cycloalkyl, C_{2-6} dialkylcarboxamido, halogen, C_{1-6} haloalkoxy, C_{1-6} haloalkyl, C_{1-6} haloalkylsulfinyl, C_{1-6} haloalkylsulfonyl, C_{1-6} haloalkylthio, hydroxyl, nitro and thiol.

51. The compound according to claim 1 wherein R_2 is C_{2-6} alkenyl optionally substituted with 1, 2, 3, 4 or 5 substituents selected independently from the group consisting of C_{1-6} alkoxy, C_{1-6} alkyl, carboxy, cyano, halogen, C_{1-6} haloalkoxy, and C_{1-6} haloalkyl.

52. The compound according to claim 1 wherein R_2 is C_{1-6} haloalkyl optionally substituted with 1, 2, 3, 4 or 5 substituents selected independently from the group consisting of C_{1-6} acyl, acyloxy, C_{2-6} alkenyl, C_{1-6} alkoxy, C_{1-6} alkyl, C_{1-6} alkylcarboxamido, C_{2-6} alkynyl, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonyl, C_{1-6} alkylthio, C_{1-6} alkylureyl, amino, C_{1-6} alkylamino, C_{2-6} dialkylamino, carbo-C_{1-6}-alkoxy, carboxy, cyano, C_{3-6} cycloalkyl, C_{2-6} dialkylcarboxamido, halogen, C_{1-6} haloalkoxy, C_{1-6} haloalkylsulfinyl, C_{1-6} haloalkylsulfonyl, C_{1-6} haloalkylthio, hydroxyl, nitro and thiol.

53. The compound according to claim 1 wherein R_2 is C_{1-6} haloalkyl optionally substituted with 1, 2, 3, 4 or 5 substituents selected independently from the group consisting of C_{1-6} alkoxy, C_{1-6} alkyl, carboxy, cyano, halogen, and C_{1-6} haloalkoxy.

54. The compound according to any one of claims 1 to 53 wherein A is C_{1-3} alkylene optionally substituted with 1, 2, 3 or 4 substituents selected independently from the group consisting of C_{1-6} alkoxy, C_{1-6} alkyl, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonyl, amino, C_{1-6} alkylamino, C_{2-6} dialkylamino, carbo-C_{1-6}-alkoxy, carboxy, cyano, C_{3-6} cycloalkyl, halogen, C_{1-6} haloalkoxy, C_{1-6} haloalkyl, C_{1-6} haloalkylsulfinyl, C_{1-6} haloalkylsulfonyl, C_{1-6} haloalkylthio and hydroxyl.

55. The compound according to any one of claims 1 to 53 wherein A is C_{1-3} alkylene optionally substituted with 1, 2, 3 or 4 substituents selected independently from the group consisting of C_{1-6} alkoxy, C_{1-6} alkyl, carbo-C_{1-6}-alkoxy, carboxy, cyano, halogen, C_{1-6} haloalkoxy, C_{1-6} haloalkyl and hydroxyl.

56. The compound according to any one of claims 1 to 53 wherein A is C_{1-3} alkylene optionally substituted with 1, 2, 3 or 4 substituents selected independently from the group consisting of C_{1-6} alkoxy, C_{1-6} alkyl, carboxy, cyano, halogen and C_{1-6} haloalkyl.

57. The compound according to any one of claims 1 to 53 wherein A is $-CH_2-$, $-CH(CH_3)-$, $-C(CH_3)_2-$ or $-CH_2CH_2-$.

58. The compound according to any one of claims 1 to 57 wherein B is C_{1-3} alkylene optionally substituted with 1, 2, 3 or 4 substituents selected independently from the group consisting of C_{1-6} alkoxy, C_{1-6} alkyl, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonyl, amino, C_{1-6} alkylamino, C_{2-6} dialkylamino, carbo-C_{1-6}-alkoxy, carboxy, cyano, C_{3-6} cycloalkyl, halogen, C_{1-6} haloalkoxy, C_{1-6} haloalkyl, C_{1-6} haloalkylsulfinyl, C_{1-6} haloalkylsulfonyl, C_{1-6} haloalkylthio and hydroxyl.

59. The compound according to any one of claims 1 to 57 wherein B is C_{1-3} alkylene optionally substituted with 1, 2, 3 or 4 substituents selected independently from the group consisting of C_{1-6} alkoxy, C_{1-6} alkyl, carbo-C_{1-6}-alkoxy, carboxy, cyano, halogen, C_{1-6} haloalkoxy, C_{1-6} haloalkyl and hydroxyl.

60. The compound according to any one of claims 1 to 57 wherein B is C_{1-3} alkylene optionally substituted with 1, 2, 3 or 4 substituents selected independently from the group consisting of C_{1-6} alkoxy, C_{1-6} alkyl, carboxy, cyano, halogen and C_{1-6} haloalkyl.

61. The compound according to any one of claims 1 to 57 wherein B is $-CH_2-$, $-CH(CH_3)-$, $-C(CH_3)_2-$ or $-CH_2CH_2-$.

62. The compound according to any one of claims 1 to 57 wherein B is a bond.

63. The compound according to any one of claims 1 to 62 wherein R_3 is selected from the group consisting of H, C_{1-6} alkoxy, C_{1-6} alkyl, cyano, C_{3-6} cycloalkyl, halogen, C_{1-6} haloalkoxy, C_{1-6} haloalkyl, hydroxyl, nitro and thiol.

64. The compound according to any one of claims 1 to 62 wherein R_3 is selected from the group consisting of H, C_{1-6} alkyl, cyano, halogen, C_{1-6} haloalkyl, hydroxyl and nitro.

65. The compound according to any one of claims 1 to 62 wherein R_3 is selected from the group consisting of H, $-CH_3$, $-CH_2CH_3$, cyano, F, Cl, Br, CF_3 and hydroxyl.

66. The compound according to any one of claims 1 to 62 wherein R_3 is H.

67. The compound according to any one of claims 1 to 62 wherein R_3 is F.

68. The compound according to any one of claims 1 to 67 wherein R_4 is C_{1-6} alkyl.

69. The compound according to any one of claims 1 to 67 wherein R_4 is selected from the group consisting of $-CH_3$, $-CH_2CH_3$, $-(CH_2)_2CH_3$, $-(CH_2)_3CH_3$, $-(CH_2)_4CH_3$, $-(CH_2)_5CH_3$, and $-(CH_2)_6CH_3$.

70. The compound according to any one of claims 1 to 67 wherein R_4 is H.

71. The compound according to claim 1 wherein:

R_1-A together is benzyl, sec-butyl, 1-methyl-butyl, thiophen-3-ylmethyl, 5-bromo-thiophen-2-ylmethyl, propyl, cyclopropylmethyl, 3-methyl-butyl, 3-methyl-but-2-enyl, cyclohexylmethyl, phenethyl, hexyl, benzo[1,3]dioxol-4-ylmethyl, thiophen-2-ylmethyl, 5-methyl-thiophen-2-ylmethyl, furan-3-ylmethyl, 4-fluoro-benzyl, 3-fluoro-benzyl, or 2-fluoro-benzyl;

R_2-B together is H, benzyl, propyl, cyclopropylmethyl, 3-methyl-butyl, 3-methyl-but-2-enyl, cyclohexylmethyl, phenethyl, hexyl, benzo[1,3]dioxol-4-ylmethyl, thiophen-2-ylmethyl, 5-methyl-thiophen-2-ylmethyl, furan-3-ylmethyl, 5-bromo-thiophen-2-ylmethyl, 4-fluoro-benzyl, 3-fluoro-benzyl, 2-fluoro-benzyl, or furan-2-ylmethyl;

R_3 is H or F; and

R_4 is H.

72. The compound according to claim 1 having the name:

5-Benzylamino-1H-pyrazole-3-carboxylic acid;

5-sec-Butylamino-1H-pyrazole-3-carboxylic acid;

5-(1-Methyl-butylamino)-1H-pyrazole-3-carboxylic acid;

5-[(Thiophen-3-ylmethyl)-amino]-1H-pyrazole-3-carboxylic acid;

5-[(5-Bromo-thiophen-2-ylmethyl)-amino]-1H-pyrazole-3-carboxylic acid;

5-Dibenzylamino-1H-pyrazole-3-carboxylic acid;

5-Dipropylamino-1H-pyrazole-3-carboxylic acid;

5-(Bis-thiophen-3-ylmethyl-amino)-1H-pyrazole-3-carboxylic acid;

5-(Bis-cyclopropylmethyl-amino)-1H-pyrrole-3-carboxylic acid;

5-[Bis-(3-methyl-butyl)-amino]-1H-pyrrole-3-carboxylic acid;

5-[Bis-(3-methyl-but-2-enyl)-amino]-1H-pyrrole-3-carboxylic acid;

5-(Bis-cyclohexylmethyl-amino)-1H-pyrazole-3-carboxylic acid;

5-Diphenethylamino-1H-pyrazole-3-carboxylic acid;

5-Dihexylamino-1H-pyrazole-3-carboxylic acid;

5-(Bis-benzo[1,3]dioxol-4-ylmethyl-amino)-1H-pyrazole-3-carboxylic acid;

5-(Bis-thiophen-2-ylmethyl-amino)-1H-pyrazole-3-carboxylic acid;

5-[Bis-(5-methyl-thiophen-2-ylmethyl)-amino]-1H-pyrazole-3-carboxylic acid;

5-(Bis-furan-3-ylmethyl-amino)-1H-pyrazole-3-carboxylic acid;

5-[Bis-(5-bromo-thiophen-2-ylmethyl)-amino]-1H-pyrazole-3-carboxylic acid;

5-[Bis-(4-fluoro-benzyl)-amino]-1H-pyrazole-3-carboxylic acid;

5-[Bis-(3-fluoro-benzyl)-amino]-1H-pyrazole-3-carboxylic acid;

5-[Bis-(2-fluoro-benzyl)-amino]-1H-pyrazole-3-carboxylic acid;

5-(Benzyl-thiophen-3-ylmethyl-amino)-1H-pyrazole-3-carboxylic acid;

5-[(4-Fluoro-benzyl)-thiophen-3-ylmethyl-amino]-1H-pyrazole-3-carboxylic acid;

5-(Thiophen-2-ylmethyl-thiophen-3-ylmethyl-amino)-1H-pyrazole-3-carboxylic acid;

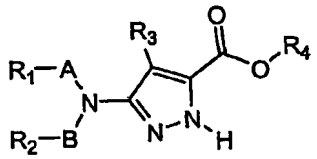
5-(Furan-2-ylmethyl-thiophen-3-ylmethyl-amino)-1H-pyrazole-3-carboxylic acid; and

5-(Furan-3-ylmethyl-thiophen-3-ylmethyl-amino)-1H-pyrazole-3-carboxylic acid;

or a pharmaceutically acceptable salt thereof.

73. A pharmaceutical composition comprising a compound according to any one of claims 1 to 73 in combination with a pharmaceutically acceptable carrier.

74. A pharmaceutical composition comprising a compound of Formula (I) in combination with a pharmaceutically acceptable carrier,



(I)

or a pharmaceutically acceptable salt, solvate or hydrate thereof;

wherein:

A is a C_{1-3} alkylene optionally substituted with 1, 2, 3, or 4 substituents selected independently from the group consisting of C_{1-6} alkoxy, C_{1-6} alkyl, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonyl, amino, C_{1-6} alkylamino, C_{2-6} dialkylamino, carbo-C_{1-6}-alkoxy, carboxy, cyano, C_{3-6} cycloalkyl, halogen, C_{1-6} haloalkoxy, C_{1-6} haloalkyl, C_{1-6} haloalkylsulfinyl, C_{1-6} haloalkylsulfonyl, C_{1-6} haloalkylthio and hydroxyl;

B is a C_{1-3} alkylene optionally substituted with 1, 2, 3, or 4 substituents selected independently from the group consisting of C_{1-6} alkoxy, C_{1-6} alkyl, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonyl, amino, C_{1-6} alkylamino, C_{2-6} dialkylamino, carbo-C_{1-6}-alkoxy, carboxy,

cyano, C_{3-6} cycloalkyl, halogen, C_{1-6} haloalkoxy, C_{1-6} haloalkyl, C_{1-6} haloalkylsulfinyl, C_{1-6} haloalkylsulfonyl, C_{1-6} haloalkylthio and hydroxyl, or B is a bond;

R_1 is H, aryl, heteroaryl, C_{1-6} alkyl, C_{3-7} cycloalkyl, C_{2-6} alkenyl, or C_{1-6} haloalkyl, wherein said R_1 is optionally substituted with 1, 2, 3, 4, or 5 substituents selected independently from the group consisting of C_{1-6} acyl, acyloxy, C_{2-6} alkenyl, C_{1-6} alkoxy, C_{1-6} alkyl, C_{1-6} alkylcarboxamido, C_{2-6} alkynyl, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonyl, C_{1-6} alkylthio, C_{1-6} alkylureyl, amino, C_{1-6} alkylamino, C_{2-6} dialkylamino, carbo-C_{1-6}-alkoxy, carboxy, cyano, C_{3-6} cycloalkyl, C_{2-6} dialkylcarboxamido, halogen, C_{1-6} haloalkoxy, C_{1-6} haloalkyl, C_{1-6} haloalkylsulfinyl, C_{1-6} haloalkylsulfonyl, C_{1-6} haloalkylthio, hydroxyl, nitro and thiol, or two adjacent substituents together with the carbon atoms to which they are bonded form a C_{5-7} cycloalkyl or C_{5-7} heterocycloalkyl optionally substituted with 1, 2, 3, or 4 halogen atoms;

R_2 is H, aryl, heteroaryl, C_{1-6} alkyl, C_{3-7} cycloalkyl, C_{2-6} alkenyl, or C_{1-6} haloalkyl, wherein said R_2 is optionally substituted with 1, 2, 3, 4, or 5 substituents selected independently from the group consisting of C_{1-6} acyl, acyloxy, C_{2-6} alkenyl, C_{1-6} alkoxy, C_{1-6} alkyl, C_{1-6} alkylcarboxamido, C_{2-6} alkynyl, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonyl, C_{1-6} alkylthio, C_{1-6} alkylureyl, amino, C_{1-6} alkylamino, C_{2-6} dialkylamino, carbo-C_{1-6}-alkoxy, carboxy, cyano, C_{3-6} cycloalkyl, C_{2-6} dialkylcarboxamido, halogen, C_{1-6} haloalkoxy, C_{1-6} haloalkyl, C_{1-6} haloalkylsulfinyl, C_{1-6} haloalkylsulfonyl, C_{1-6} haloalkylthio, hydroxyl, nitro and thiol, or two adjacent substituents together with the carbon atoms to which they are bonded form a C_{5-7} cycloalkyl or C_{5-7} heterocycloalkyl optionally substituted with 1, 2, 3, or 4 halogen atoms;

R_3 is selected from the group consisting of H, C_{1-6} acyl, acyloxy, C_{2-6} alkenyl, C_{1-6} alkoxy, C_{1-6} alkyl, C_{1-6} alkylcarboxamido, C_{2-6} alkynyl, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonyl, C_{1-6} alkylthio, C_{1-6} alkylureyl, amino, C_{1-6} alkylamino, C_{2-6} dialkylamino, carbo-C_{1-6}-alkoxy, carboxy, cyano, C_{3-6} cycloalkyl, C_{2-6} dialkylcarboxamido, halogen, C_{1-6} haloalkoxy, C_{1-6} haloalkyl, C_{1-6} haloalkylsulfinyl, C_{1-6} haloalkylsulfonyl, C_{1-6} haloalkylthio, hydroxyl, nitro and thiol; and

R_4 is H or C_{1-6} alkyl.

75. A method of modulating a **RUP38** receptor comprising contacting said receptor with an effective amount of a compound according to any one of claims 1 to 72.

76. The method according to claim 74 wherein said compound is an agonist of said receptor.

77. A method of modulating a **RUP38** receptor in an individual comprising contacting said receptor with an effective amount of a compound according to any one of claims 1 to 72.

78. The method according to claim 77 wherein said modulation treats a metabolic-related disorder.

79. A method of modulating **RUP38** receptor function in a cell, tissue or individual comprising contacting said cell, tissue or individual with an effective amount of a compound according to any one of claims 1 to 72 or a pharmaceutical composition according to claim 73 or 74.

80. The method according to claim 79 wherein said **RUP38** receptor function is associated with a metabolic-related disorder.

81. A method of treatment of a metabolic-related disorder comprising administering to an individual in need of such treatment a therapeutically effective amount of a compound according to any one of claims 1 to 72 or a pharmaceutical composition according to claim 73 or 74.

82. The method according to any one of claims 78, 80 and 81 wherein said metabolic-related disorder is selected from the group consisting of dyslipidemia, atherosclerosis, coronary heart disease, insulin resistance, obesity, impaired glucose tolerance, atheromatous disease, hypertension, stroke, Syndrome X, heart disease, type 2 diabetes, hypo-HDL related atherosclerotic risk, ischemic cerebrovascular disease, peripheral vascular disease, stroke, and myocardial infarction.

83. The method according to claim 82 wherein said metabolic-related disorder is selected from the group consisting of dyslipidemia, atherosclerosis, coronary heart disease, insulin resistance and type 2 diabetes.

84. The method according to claim 82 wherein said metabolic-related disorder is dyslipidemia.

85. A method of raising HDL cholesterol levels in an individual comprising administering to said individual a therapeutically effective amount of a compound according to any one of claims 1 to 72 or a pharmaceutical composition according to claim 73 or 74.

86. The method according to any one of claims 79 to 85 wherein said individual is a mammal.

87. The method according to claim 86 wherein said mammal is a human.

88. A method of producing a pharmaceutical composition comprising admixing a compound according to any one of claims 1 to 72 and a pharmaceutically acceptable carrier.

89. Use of a compound according to any one of claims 1 to 72 for production of a medicament for use in treatment of a metabolic-related disorder.

90. A compound according to any one of claims 1 to 72 or a pharmaceutical composition according to claim 73 or 74 for use in a method of treatment of the human or animal body by therapy.

91. A compound according to any one of claims 1 to 72 or a pharmaceutical composition according to claim 73 or 74 for use in a method of treatment of a metabolic-related disorder of the human or animal body by therapy.

92. The compound according to claim 91 wherein said metabolic-related disorder is selected from the group consisting of dyslipidemia, atherosclerosis, coronary heart disease, insulin resistance, obesity, impaired glucose tolerance, atheromatous disease, hypertension, stroke, Syndrome X, heart disease, type 2 diabetes, hypo-HDL related atherosclerotic risk, ischemic cerebrovascular disease, peripheral vascular disease, stroke, and myocardial infarction.

93. The compound according claim 91 wherein said metabolic-related disorder is selected from the group consisting of dyslipidemia, atherosclerosis, coronary heart disease, insulin resistance and type 2 diabetes.

94. The compound according claim 91 wherein said metabolic-related disorder is dyslipidemia.

95. A compound according to any one of claims 1 to 72 or a pharmaceutical composition according to claim 73 or 74 for use in a method of raising HDL cholesterol levels of the human or animal body by therapy.

96. The method of producing a pharmaceutical composition comprising admixing at least one compound of any one of claims 1 to 72 and a pharmaceutically acceptable carrier.

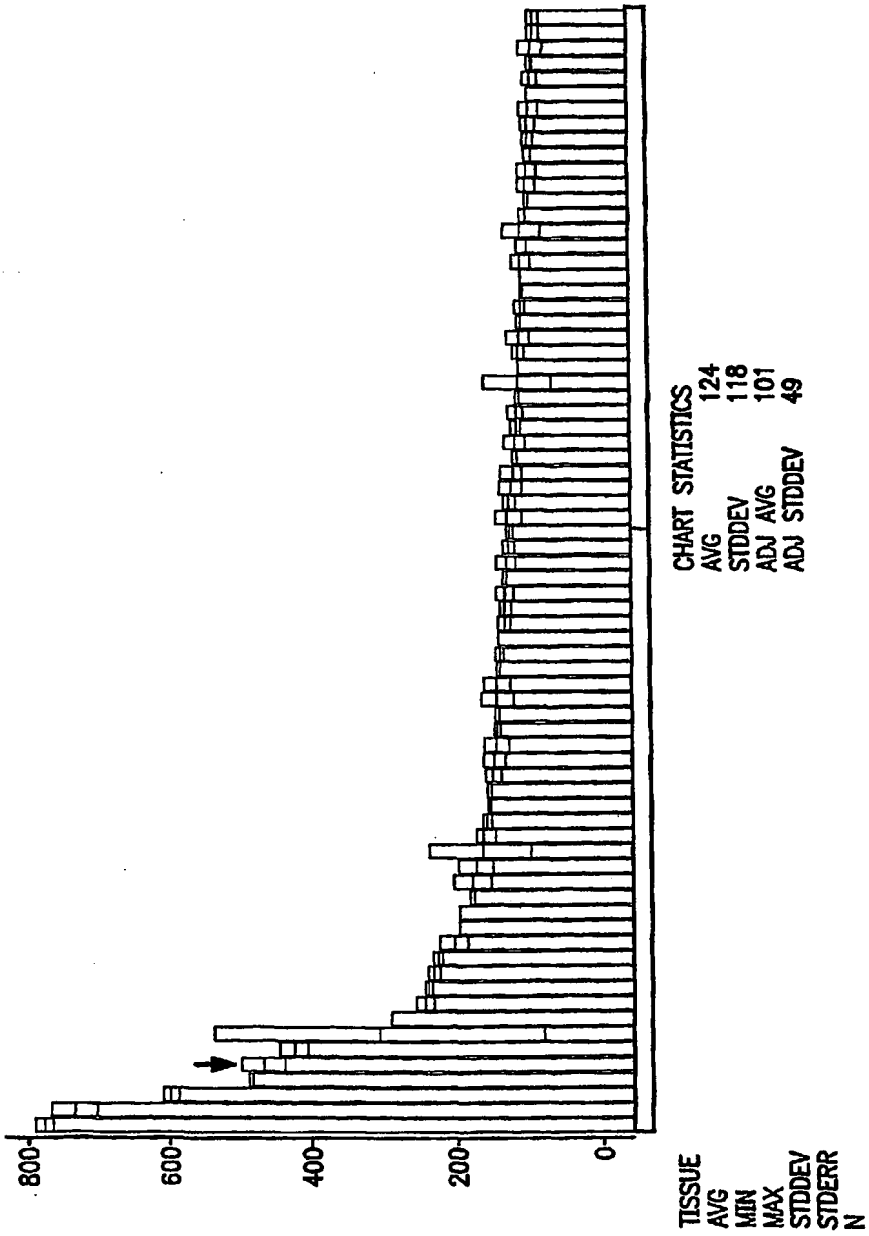

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FIG. 1

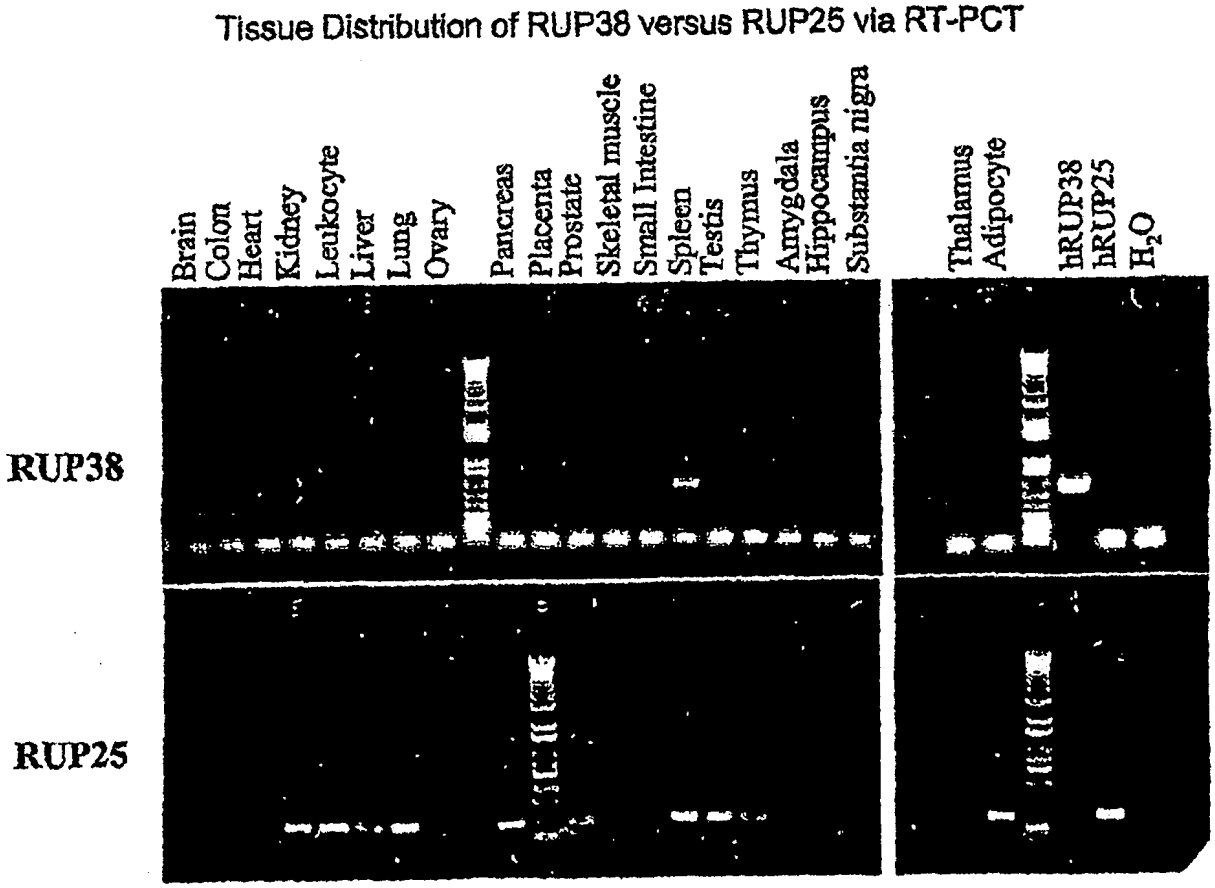

Tissue Distribution of RUP38 versus RUP25 via RT-PCT
Brain
Colon
Heart
Kidney
Leukocyte
Liver
Lung
Ovary
Pancreas
Placenta
Prostate
Skeletal muscle
Small Intestine
Spleen
Testis
Thymus
Amygdala
Hippocampus
Substantia nigra
Thalamus
Adipocyte
hRUP38
hRUP25
H_2O
RUP38
RUP25

FIG. 2

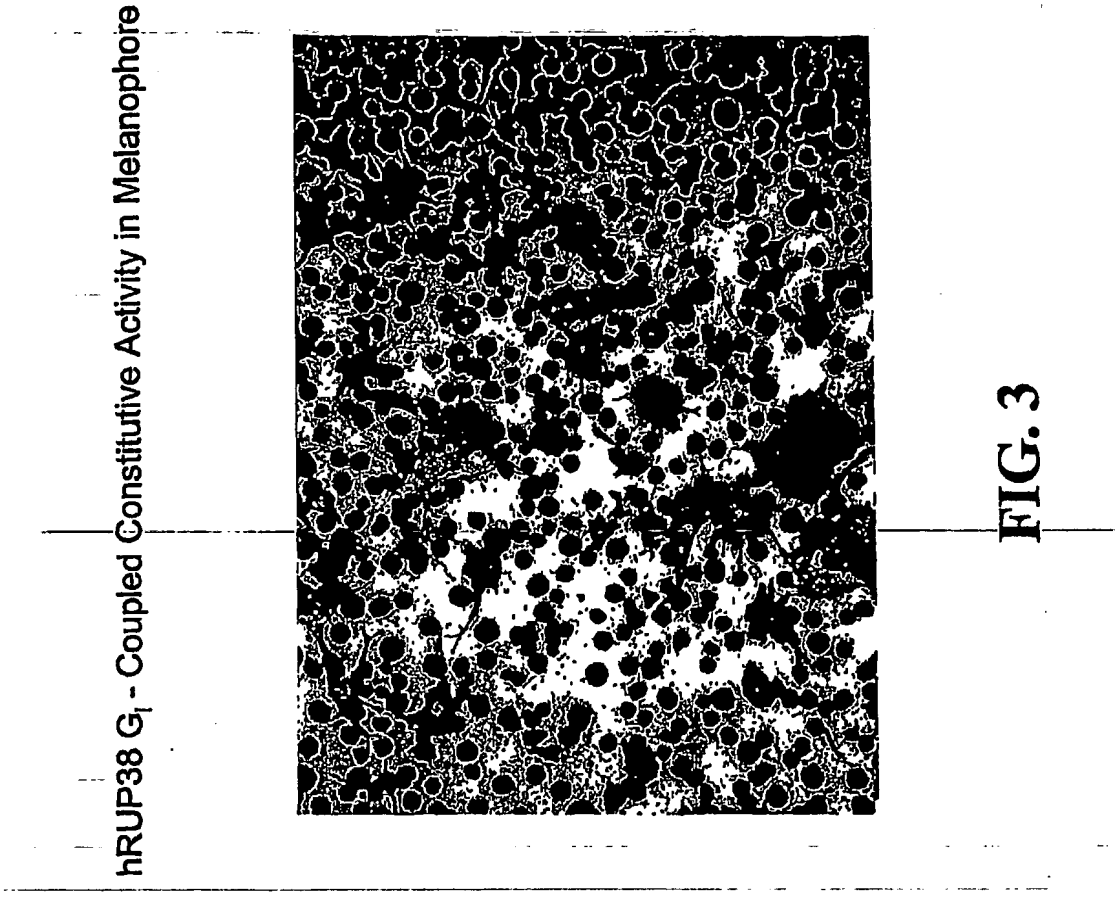
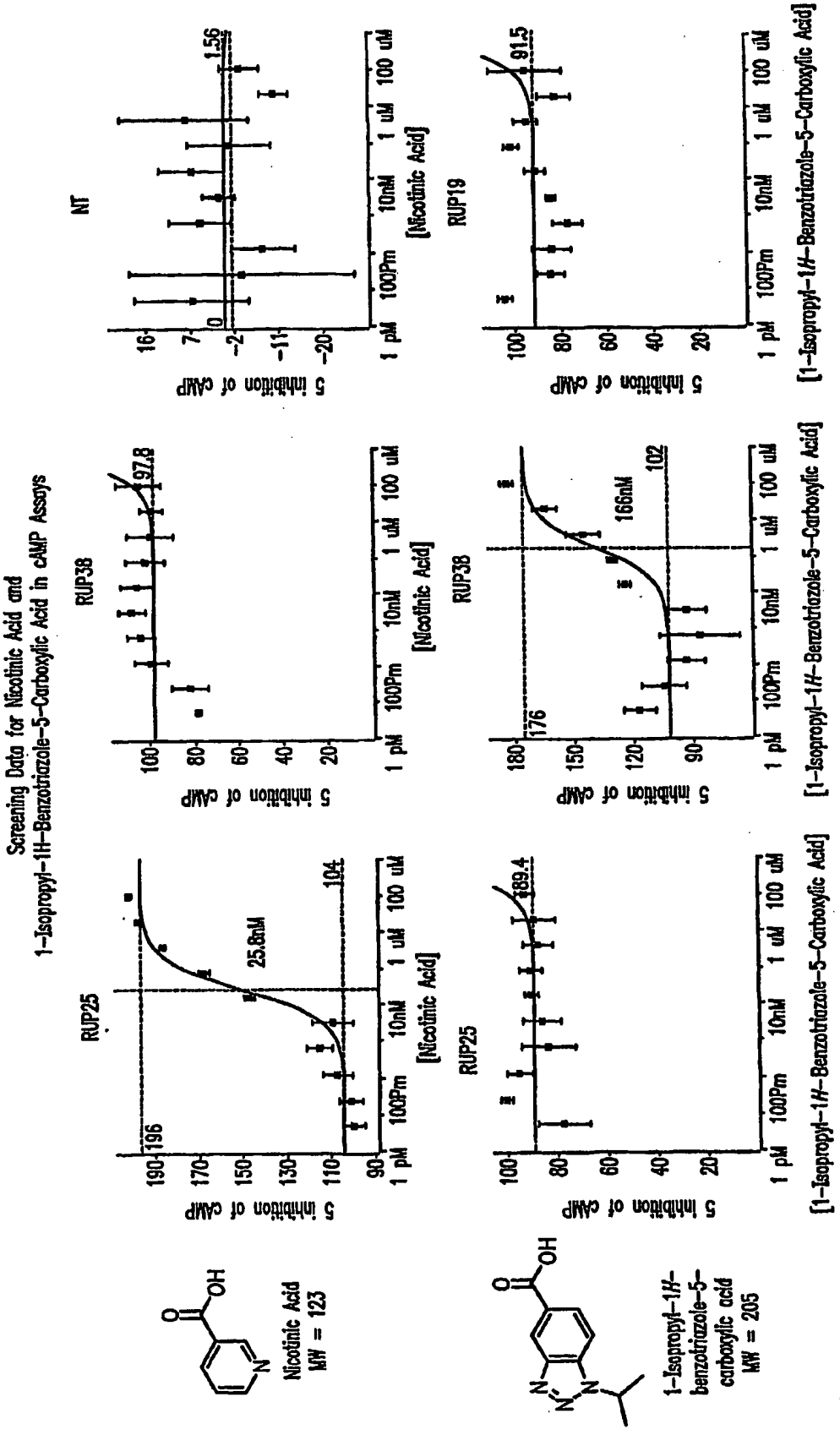


FIG. 3


Screening Data for Nicotinic Acid and
1-Isopropyl-1H-Benzotriazole-5-Carboxylic Acid in cAMP Assays
RUP25
RUP38
NT
RUP19
RUP25
RUP38
5 inhibition of cAMP
[Nicotinic Acid]
[1-Isopropyl-1H-Benzotriazole-5-Carboxylic Acid]
1 pM
100Pm
10nM
1 uM
100 uM
196
25.8nM
104
197.8
1.56
91.5
189.4
166nM
102
176
Nicotinic Acid
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benzotriazole-5-
carboxylic acid
MW = 205

FIG. 4

114.WO1.ST25.txt
SEQUENCE LISTING

<110> Arena Pharmaceuticals, Inc.
Skinner, Philip J.
Semple, Graeme
Webb, Peter

<120> 5-Aminopyrazole Carboxylic Acid Derivatives and Methods of Treatment of Metabolic-Related Disorders Thereof

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INTERNATIONAL SEARCH REPORT

International application No
PCT/US2006/019730

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D231/38 A61K31/415 A61P3/00 A61P3/04 A61P3/06
A61P3/10

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2004/032928 A (ARENA PHARMACEUTICALS, INC) 22 April 2004 (2004-04-22) claims 1,34	1-96
A	US 2004/142377 A1 (ARENA PHARMACEUTICALS, INC) 22 July 2004 (2004-07-22) page 3, paragraph 18 - paragraph 26 page 3, paragraph 22 page 20, paragraph 377 page 85, paragraph 2349	1-96
A	WO 01/57034 A (BRISTOL-MYERS SQUIBB COMPANY) 9 August 2001 (2001-08-09) page 14, line 12 - line 21 claim 1	1-96

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
2 October 2006	11/10/2006

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Cortés, José

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2006/019730

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 75-87 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

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